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Анализ на апостериорната грешка за апроксимация с редуциран базис на две параболични задачи за растеж на тумори

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A posteriori error analysis for a reduced-basis approximation of two parabolic problems for tumour growth

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Abstract

This work presents a theoretical analysis for an *a posteriori* error estimate for a reduced-basis approximation of the solution for two parametrised parabolic problems. Their motivation is in mathematical oncology and they describe a) a model for brain tumour growth [14] and b) a model for phenotype evolution of a tumour based on [3, 13], with the free parameter being the therapeutic dose. The discretisation of the problems in space is realised by the finite element method, and the numerical integration uses a first-order IMEX scheme due to model b) being a integro-differental problem. The obtained *a posteriori* error estimatefor the approximation error between the numerical solution and the reduced basis solution gives the opportunity for constructing a reduced basis for the solution manifold by combining a proper orthogonal decomposition of the temporal trajectories and a greedy algorithm over the parameter range, as has been done in the case of explicit or implicit integration of linear parabolic problems [8, 10].

Резюме

Представен е теоретичен анализ на *апостериорна* оценка на грешката при приближено решаване на две параметрични параболични задачи по метода на редуцирания базис. Мотивацията им идва от математическата онкология и те описват а) модел за растеж на мозъчен тумор от [14] и б) модел за фенотипна еволюция в тумор, основан на статиите [3, 13], със свободен параметър терапевтична доза. Дискретизацията на задачата в пространството е осъществена с помощта на метода на крайните елементи, а за числеността интегриране е използвана IMEX схема от първи ред, тъй като моделът б) е интегро-диференциален. Получената *апостериорна* оценка на грешката на апроксимация на числеността решение с решението по метода на редуцирания базис дава възможност за построение на редуциран базис на множеството от решенията чрез съчетаване на правилно ортогонално разлагане на времевите траектории и алчен алгоритъм в диапазона на параметъра, както е направено в случая на явно или неявно интегриране на линейни параболични задачи [8, 10].

Contents

Chapter 1

Introduction

Reduced basis (RB) methods are a tool for model order reduction, and are used in approximating the solutions to parametrised partial differential equation by solutions to problems of lower numerical complexity that are computationally cheaper and faster to implement. The RB methods' strength stems from the property that the set of solutions of the given high-fidelity problem typically in a finite element space of very high dimension can be approximated by linear combinations of basis elements of a subspace of much lower dimension (the reduced basis space). The possibility to achieve a approximation with reasonable accuracy of the set of solutions by means of bases in low-dimensional subspaces arises from its regularity (compactness, smoothness, analyticity) and the parametric complexity of the original problem and the regularity of the parameter-dependent terms.

To construct a good reduced basis, one relies on principal component analysis or greedy algorithms. The efficiency of the greedy algorithms relies crucially on *a posteriori estimates* for the error between the high-fidelity solution and the reduced basis solution for every parameter value. The success of the method depends on the capacity to evaluate the solution for any new free parameter value at a cost independent of the dimension of the original problem [12, 15].

Recent applications of the method [6] include applications to problems from the engineering sciences or physics and cover

- various linear and non-linear elliptic problems,
- linear parabolic problems [8, 10],
- the Navier-Stokes equations.

The method has not yet been applied to problems in biomedical applications. The difficulties involve not only the higher non-linear complexity stemming from the coupling of the variables, but also from the choice of appropriate stable time-integration schemes.

Mathematical models for tumour growth and onco-immune interactions are based on partial differential equations, integro-differential equations, cellular automata and multiscale models. Many tumour growth models involve non-local and non-linear problems related to the biological properties of the system. Some are computationally intensive in case the domain of definition requires a fine mesh to capture spatial inhomoigeneities,

or involve repetitive solving for different parameter values if the model strives to find an optimal treatment strategy among different drug regimes.

In this study we develop a theoretical framework for the *a posteriori estimator* to be used in the reduced basis method applied to parameter-dependent problems with motivation from oncology. We consider a model for tumour growth in the brain from [14]as well as a phenotype selection model under the action of chemotherapy based on models [3, 13]. The models are solved using first-order-in-time implicit-explicit (IMEX) methods and a variational formulation based on the finite element method.

1.1 Function spaces

We recall the following function spaces to be used in the analysis. Let Ω be a compact set in $\mathbb{R}^2$ or $\mathbb{R}^3$. The spaces of Lebesgue-integrable functions on Ω are defined as

- $L^1(\Omega) = \{f - \text{measurable} \mid \int_\Omega |f(\mathbf{x})|\, d\mathbf{x} < \infty\}$
- $L^2(\Omega) = \{f - \text{measurable} \mid \int_\Omega |f(\mathbf{x})|^2\, d\mathbf{x} < \infty\}$ which is a Hilbert space with inner product $\langle \cdot, \cdot \rangle$
- $L^\infty(\Omega) = \{f - \text{measurable} \mid \text{esssup}_{\mathbf{x}\in\Omega} |f(\mathbf{x})| < \infty\}$

with the standard norms.

Let the gradient $\nabla f = (\partial_x f, \partial_y f)$ if $\Omega \subset \mathbb{R}^2$, and $\nabla f = (\partial_x f, \partial_y f, \partial_z f)$ if $\Omega \subset \mathbb{R}^3$. The Sobolev space $H^1(\Omega)$ is defined as

$$H^1(\Omega) = \{f \in L^2(\Omega) | \nabla f \in [L^2(\Omega)]^d\}, \quad d = 2, 3\,.$$

$H^1(\Omega)$ is a Hilbert space with inner product inherited from the L^2-inner product:

$$\langle u, v \rangle_{H^1} \stackrel{\text{def}}{=} \langle u, v \rangle + \langle \nabla u, \nabla v \rangle\,.$$

The notation for the norm of the gradient shall be $\|\nabla f\|_{L^2} \stackrel{\text{def}}{=} (\|\partial_x f\|_{L^2} + \|\partial_y f\|_{L^2})^{1/2}$ or $(\|\partial_x f\|_{L^2} + \|\partial_y f\|_{L^2} + \|\partial_z f\|_{L^2})^{1/2}$ respectively. The H^1-norm is defined by the inner product

$$\|f\|_{h^1} = (\|f\|_{L^2}^2 + \|\nabla f\|_{L^2}^2)^{1/2}.$$

In our analysis we shall consider finite element spaces $\mathbb{V}_h \subset H^1(\Omega)$ which inherit the inner product from the Sobolev space.

The domain Ω is subjected to a triangulation $\mathcal{T}_h$ which covers it completely:

$$\bar{\Omega} = \bigcup_{\Delta_K \in \mathcal{T}_h} \Delta_K$$

Based on $\mathcal{T}_h$, a finite element space $\mathbb{V}_h$ of dimension N_h is constructed to find an approximate solution of the problem. The pair $(\mathcal{T}_h, \mathbb{V}_h)$ satisfies the classical assumptions on regularity, affine equivalence and compact support of the finite element functions [5, p. 132].

The triangulation $\mathcal{T}_h$ is also quasi-uniform [5, 16, 17] in the sense that

$$\exists \nu > 0: \quad h\nu < \min_{\Delta_K \in \mathcal{T}_h} \text{diam}(\Delta_K) \leq \max_{\Delta_K \in \mathcal{T}_h} \text{diam}(\Delta_K) \leq h\,.$$

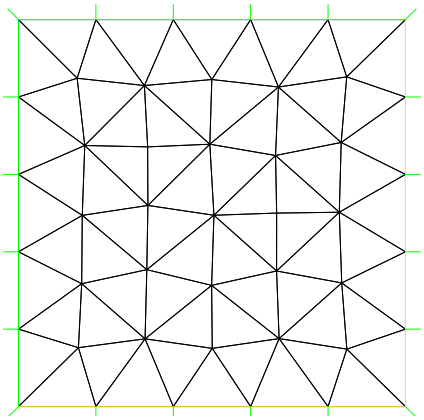

Figure 1.1: An example of a triangulation of the unit square which is regular and quasi-uniform generated in `FreeFem++` [11].

Thus, the finite element approximation space $\mathbb{V}_h$ is defined as the set of continuous functions on the closure of Ω whose restriction to the triangle is a poynomial of degree $m, m = 1, 2$:

$$\mathbb{V}_h = \{\varphi \in C(\bar{\Omega}) \ : \ \varphi|_{\Delta_K} \in \mathbb{P}_m, \forall \Delta_K \in \mathcal{T}_h\} \ .$$

The basis $\{\varphi_i\}_{i=1}^{N_h}$ of $\mathbb{V}_h$ consists of shape functions φ_i (dependent on the degree m) defined on the triangles $\Delta_K \in \mathcal{T}_h$. The literature on the construction and properties of finite element spaces is extensive and we refer to the books [2, 5, 16] for further details.

It is well known that such finite element spaces satisfy *inverse inequalities* in Sobolev space norms, and in the subsequent analysis, we will use the following inequality [5, (3.2.25)] in particular:

$$\|\nabla \phi\|_{L^2}^2 \leq \frac{c_\Omega}{h^2} \|\phi\|_{L^2}^2, \quad \forall \phi \in \mathbb{V}_h \ . \tag{1.1}$$

where the constant c_Ω depends on the domain Ω.

1.2 Parametrised parabolic problem

We are interested in solving numerically the parametrised problem

$$\partial_t u(t,x) = \mathcal{L}(u, t, x, \mu), \quad t \in (0, T_{max}], x \in \Omega \tag{1.2}$$

where the operator $\mathcal{L}$ is elliptic and depends on a free parameter μ, which takes values in a compact set $\mathcal{M}$.

We make no particular assumptions on $\mathcal{L}$ (those are problem-dependent), and so for the moment we assume that due to sufficient regularity, the exact solution of (1.2) $u(t, \cdot; \mu) \in H^1(\Omega)$ for all $t \in (0, T_{max}]$. The solution $u(\cdot; \mu)$ will depend (in a nonlinear way) on μ. The equation (1.2) is complemented by appropriate boundary conditions on $\partial\Omega$ and initial data $u(0, \cdot) = u_0 \in H^1(\Omega)$.

We seek a numerical approximation $u_h(t, x)$ of the exact solution $u(t, x)$ of (1.2) in a finite element approximation space $\mathbb{V}_h$, which comes from a variational formulation. The equation (1.2) in semi-discrete variational form is:

$$\langle \partial_t u, \phi \rangle + a(u, \phi; \mu) = \langle b(u; \mu), \phi \rangle, \quad \forall \phi \in \mathbb{V}_h \ , \tag{1.3}$$

where the inner product $\langle \cdot, \cdot \rangle$ on $\mathbb{V}_h \times \mathbb{V}_h$ is inherited from $L^2 \times L^2$ and $a(\cdot, \cdot; \mu)$ is a bilinear form on $\mathbb{V}_h \times \mathbb{V}_h$ inherited from $H^1 \times H^1$, and $b(u; \mu)$ is some advective, nonlinear (or integral) term in u, which cannot be resolved in a reasonable implicit manner.

Normally the numerical discretisation of $a(\cdot, \cdot; \mu)$ (numerical Laplacian) translates to a stiff matrix which must be solved for in an implicit manner in order to maitain the numerical stability of the integration scheme without placing severe restriction on the discretisation in time.

Hence, we resort to implicit-explicit (IMEX) schemes which take care of these issues. We fix the value μ and denote by $u_h^k(\mu)$ the approximation of $u(k\tau, \cdot)$ at the uniformly-spaced time layers $k\tau, k = 0, 1, \ldots k_{max}$ for some $\tau > 0$. $U_h(\mu)$ shall denote the numerically computed solution trajectory for the parameter μ, that is, the sequence of solutions of the parametrised parabolic problem for the parameter value μ_i (1.2) at these discrete time layers, that is $U_h(\mu_i) \stackrel{\text{def}}{=} \{u_h^k(\mu_i)\}_{k=0,1,\ldots k_{max}}$.

1.3 Time-integration IMEX schemes

We choose a uniform-in-time grid with time step τ, with nodes $t_k = k\tau, k \in \mathbb{N}$, to write out the fully discrete spatio-temporal scheme. For sake of shortness, we drop the μ and set

$$b^{(k)}(\phi) \stackrel{\text{def}}{=} \langle b(u_k), \phi \rangle, \quad k \in \mathbb{N}.$$

The trajectory $U_h(\mu)$ which approximates the exact solution to the parabolic problem (1.3) obtained by the above numerical scheme, shall be referred to as a *high-fidelity solution*.

An overview of IMEX schemes is done in [1], which we recall in more detail.

If (1.3) were a pure reaction-diffusion problem, *first-order-in-time* schemes could be a reasonable choice. The first-order-in-time IMEX scheme from [1], which we denote here as IMEX-θ scheme (with parameter $0 \leq \theta \leq 1$), writes as

$$\langle u_{k+1}, \phi \rangle + \tau\theta a(u_{k+1}, \phi) = \langle u_k, \phi \rangle + \tau b^{(k)}(\phi) - \tau(1-\theta)a(u_k, \phi) \tag{1.4}$$

Note that the choice $\theta = 0$ is a fully explicit scheme (forward Euler), and the choice $\theta = 1$ represents the semi-implicit backward differentiation formula (semi-implicit BDF). Note further that the choice $\theta = \frac{1}{2}$ would be the Crank-Nicholson scheme whenever $b^{(k)}(u) = 0$. Thus, the IMEX-θ scheme *is not the same* as the θ-scheme for parabolic problems [16, Chapter 11.3].

Among the second-order-in-time schemes proposed in [1] are

1. Crank-Nicholson Adams-Bashford (CNAB)

$$\langle u_{k+1}, \phi \rangle + \frac{\tau}{2} a(u_{k+1}, \phi) = \langle u_k, \phi \rangle - \frac{\tau}{2} a(u_k, \phi) + \frac{3\tau}{2} b^{(k)}(\phi) - \frac{\tau}{2} b^{(k-1)}(\phi) \,, \tag{1.5}$$

2. modified CNAB (MCNAB)

$$\begin{aligned} \langle u_{k+1}, \phi \rangle + \frac{9\tau}{16} a(u_{k+1}, \phi) = \langle u_k, \phi \rangle - \frac{3\tau}{8} a(u_k, \phi) - \frac{\tau}{16} a(u_{k-1}, \phi) \\ + \frac{3\tau}{2} b_k(\phi) - \frac{\tau}{2} b_{k-1}(\phi) \,, \end{aligned} \tag{1.6}$$

3. Semi-backward differentiation formula (SBDF)

$$\frac{3}{2}\langle u_{k+1},\phi\rangle + \tau a(u_{k+1},\phi) = 2\langle u_k,\phi\rangle - \frac{1}{2}\langle u_{k-1},\phi\rangle + 2\tau b_k(\phi) - \tau b_{k-1}(\phi)\ . \qquad (1.7)$$

The schemes (1.5)-(1.7) will prove to be more useful in applications to problems with advective terms, such as the model (3.2).

1.4 Reduced basis approximation of the solution

If the parabolic problem (1.3) needs to be solved in a *multi-query context* (e.g. for the needs of a optimisation problem), for many values of the parameter μ, a direct approach may turn out to be too expensive numerically. The structure of the solution manifold $\mathfrak{U}_h = \cup_{\mu\in\mathcal{M}} U_h(\mu)$ can be exploited to reduce the complexity if it is a compact set. In particular, we quote the following

> "A central assumption in the development of any reduced model is that the solution manifold is of low dimension, i.e., that the span of a low number of appropriately chosen basis functions represents the solution manifold with a small error."
>
> – [12, p.28]

We thus seek an approximation of the high-fidelity solutions $U_h(\mu) = \{u_h^k(\mu)\}_k$ of the parabolic problem (1.3) in $\mathbb{V}_h$ inside a lower-dimensional subspace of $\mathbb{V}_h$. Our aim is to approximate the solution $U_h(\mu)$ by a *reduced basis (RB) solution* $U_{\rm rb}(\mu)$, a method that is essentially a Galerkin-type projection.

$U_{\rm rb}(\mu)$ is given as a linear combination of elements of a reduced basis $\{\xi_i\}_{i=1}^N$ for a subspace of $\mathbb{V}_h$, called a *reduced basis space* $\mathbb{V}_{\rm rb}^N$. This subspace is extracted from the solutions of the high-fidelity problem some carefully chosen subset of parameters $\mathcal{M}_* \subset \mathcal{M}$, with $\mathbb{V}_{\rm rb}^N \subset \cup_{\mu\in\mathcal{M}_*} U_h(\mu)$. As long as the approximation error between the high-fidelity solution $U_h(\mu)$ and the reduced basis solution $U_{\rm rb}(\mu)$ remains sufficiently small for every value of μ, the reduced basis approximation to the high-fidelity solution has a guaranteed accuracy [12, 15]. The estimation of the approximation error is central to the performance of the method.

In algebraic terms, if $\mathbb{V} \in \mathbb{R}^{N\times N_h}$ is the matrix whose columns are formed by the reduced basis elements $\{\xi_i\}_{i=1}^N$, the RB method seeks an approximation of $u_h^k(\mu)$ of the form $\mathbb{V}\mathbf{u}_k^\mu, \mathbf{u}_k^\mu \in \mathbb{R}^N$. In the case of IMEX scheme, $u_h^k(\mu)$ typically results from solving a linear problem at every time layer k,

$$\mathcal{A}_k(\mu)u_h^k(\mu) = f^{(k-1)}(\mu)\ .$$

From the point of view of the reduced basis, this is equivalent to solving

$$\mathbb{A}_k(\mu)\mathbf{u}_k^\mu = \mathbf{f}^{(k-1)}(\mu)$$

where the new stiffness matrix $\mathbb{A}_k(\mu) = \mathbb{V}^T\mathcal{A}_k(\mu)\mathbb{V}$ and the new load vector $\mathbf{f}^{(k-1)}(\mu) = \mathbb{V}^T f^{(k-1)}(\mu)$ are obtained as projections onto the RB space or operators on it. Observe that $\mathbb{A}_k(\mu) \in \mathbb{R}^{N\times N}, \mathbf{f}^{(k-1)}(\mu) \in \mathbb{R}^N$, so the problem dimension has been reduced.

Such a method will be efficient as long as the stiffness matrices $\mathbb{A}_k(\mu)$, the load vectors $\mathbf{f}^{(k-1)}(\mu)$ and the approximation error estimators of the reduced basis approximation (1.3) have an affine dependence on the parameter μ [15]. Indeed, if this is possible, then they can be assembled via parameter-independent precomputed building blocks for each new value of μ. In this way, if repeated queries for the solution of (1.3) for different μ are needed, they can be computed at a lower computational cost. Furthermore, we want the computation of approximate solution in $\mathbb{V}_{\mathrm{rb}}$ for the different parameter values μ to remain independent of $\dim \mathbb{V}_h$.

1.4.1 Offline and online phases

The construction of the reduced basis of least possible dimension that meets the accuracy criterion may be computationally intensive, but is done just once during the *offline stage*. Snapshot solutions of the high-fidelity problem, $u_h(\mu)$ for carefully chosen values $\mu \in \mathcal{M}_*$ of the parameter will be orthonormalised to form the basis $\{\xi_i\}_{i=1}^N$ via proper orthogonal decomposition (POD) or principal component analysis (PCA) [], greedy algorithm, a combination of both [8, 9, 15, 12]. The choice of a sufficiently rich parameter sample set $\mathcal{M}_*$ can be done in by uniform sampling [15, p. 69] or a nonlinear optimisation problem [18]. At this stage all parameter-independent objects (stiffness matrices and load vectors) for (1.3) will be computed by projection onto $\mathbb{V}_{\mathrm{rb}}$ and stored.

During the *online stage* the computation of the RB solution for a new parameter value shall involve the computation of the respective RB objects (stiffness matrices and load vectors) from those obtained during the offline phase. Next the expansion coefficients $\mathbf{u}_k^\mu$ will be computed and the RB solution will be assembled from $\mathbb{V}\mathbf{u}_k^\mu$. It is clear that the objects computed during the offline phase and the assembled during the online phase RB objects will depend on the problem at hand. Details on the algebraic formulation of the problem for computing $\mathbf{u}_k^\mu$ for the the considered in this report parabolic problems are given in Sections 2.3.1 and 3.3.1.

The offline and online stages are summarised in the flowchart (1.2).

1.4.2 Reduced basis construction via the POD-greedy algorithm

In the reduced basis context the greedy algorithm is readily used for construction RB solutions for elliptic problems. The algorithm constructs successive elements of the basis (it basically follows a process of *basis refinement*). It enriches at every step the subspace by adding an additional reduced basis element associated to the snapshot $u_h(\mu)$ for parameter value μ that maximises the approximation error between the snapshot $u_h(\mu)$ and its projection onto the RB basis constructed thus far $u_{\mathrm{rb}}(\mu)$,

$$\mu = \arg\max_{\mu\in\mathcal{M}} \|u_h(\mu) - u_{\mathrm{rb}}(\mu)\|_{\mathbb{V}_h}$$

and is computationally efficient as long as the approximation error $\|u_h(\mu)-u_{\mathrm{rb}}(\mu)\|_{\mathbb{V}_h}$ can be estimated easily by an estimator $\Delta(\mu)$. This leads to a sequence of nested subspaces of $\mathbb{V}_{\mathrm{rb}}$ until the desired accuracy between the truth and the reduced basis solution is reached.

Following [12, 15], we shall use a sufficiently dense subset of $\mathcal{M}$ as a training sample for the algorithm, and denote it by $\Xi_{train} = \{\mu_\ell\}, 1 \le \ell \le m$.

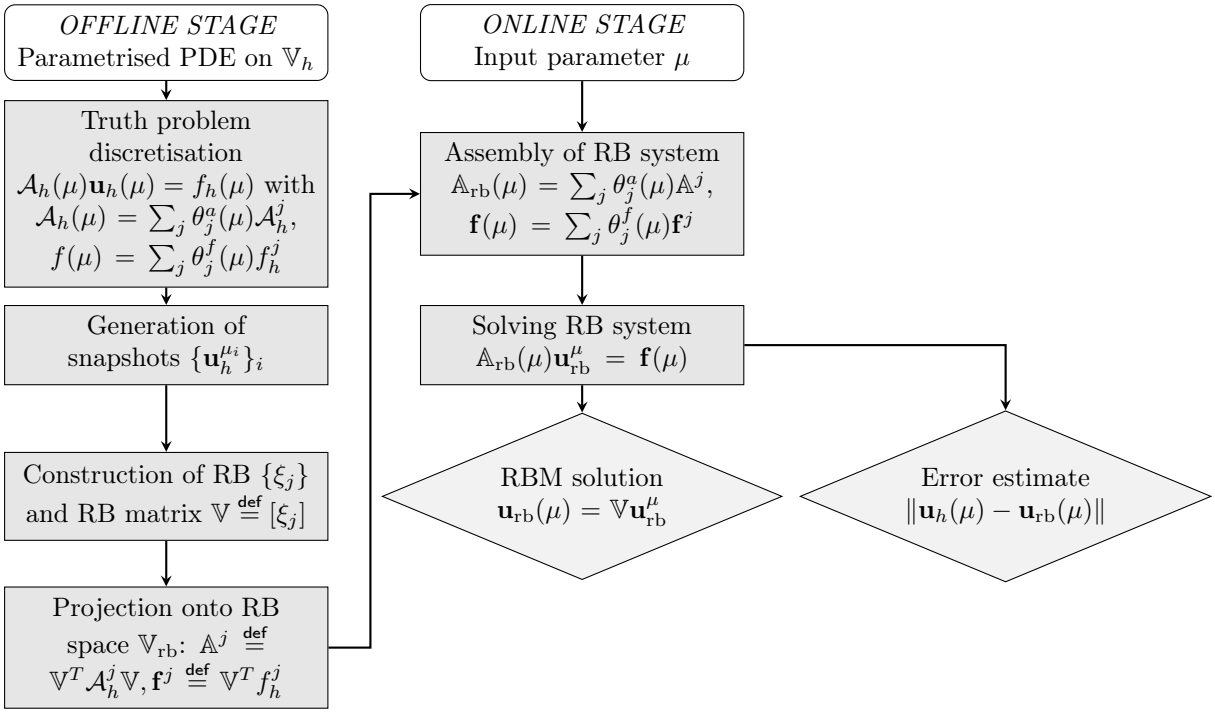

Figure 1.2: Flowchart of the reduced basis method (after [15, p. 9]).

In the context of the parabolic problem (1.2) the greedy algorithm can be complemented by a *proper orthogonal decomposition* step. This is done to minimise redundancy of storage of basis elements and to avoid possible stalling of the algorithm as discussed in [9]. Due to the fact that the solution trajectory may be convergent to some value, it is advantageous to compress it using *proper orthogonal decomposition* (POD).

We recall that the POD finds the basis $\{\zeta_j\}_{j=1}^m$ of that particular m-dimensional subspace Y of $U_h(\mu_i)$, whose basis functions solve the minimisation problem

$$\left(\frac{1}{k_{max}}\sum_{k=1}^{k_{max}} \inf_{\substack{v\in Y \\ \dim Y = m}} \|u_h^k(\mu_i) - v\|_{\mathbb{V}_h}^2\right)^{1/2} \to \min\,.$$

In this way the information contained in $U_h(\mu_i)$ is compressed before searching for the next RB element.

Here is the proposed algorithm which intertwines a POD step with a greedy step [15].

The POD-greedy algorithm:
`Input:` $\Xi_{train}, N_1, N_2 \in \mathbb{N}, N_2 < N_1, N = 0, \ell = 1, \mathcal{Z} = \varnothing, \varepsilon$
`Output:` $\mathbb{V}_{\text{rb}}, N$
`While (`$\Delta(\mu_{\ell+1}) < \varepsilon$`) do 1-7`

1. `Compute the trajectory for` μ_ℓ:

$$U_h(\mu_\ell) \leftarrow \{u_h^1(\mu_\ell), u_h^2(\mu_\ell), \dots u_h^{k_{max}}(\mu_\ell)\}$$

2. `Compress` $U(\mu_\ell)$ `and retain the` N_1 `principal nodes using the POD`:

$$\{\zeta_j\}_{j=1}^{N_1} \leftarrow \texttt{POD}(U_h(\mu_\ell), N_1)$$

3. `Enrich the basis` $\mathcal{Z} \leftarrow \mathcal{Z} \cup \{\zeta_j\}_{j=1}^{N_1}$

4. `Set` $N \leftarrow N + N_2$, `and find the` N `principal nodes` $\{\xi_j\}_{j=1}^{N} \leftarrow \texttt{POD}(\mathcal{Z}, N)$

5. $\mathbb{V}_{\mathrm{rb}} \leftarrow \mathrm{span}\{\xi_j\}_{j=1}^{N}$

6. `Set`
$$\mu_{\ell+1} := \arg \max_{\mu \in \Xi_{train}} \Delta(\mu) \, . \tag{1.8}$$

7. `Set` $\ell \leftarrow \ell + 1$

Observe on every iteration of the POD-greedy algorithm we add one more orthonormalised solution trajectory whose approximation is worst by the RB space with ℓ elements, unless the desired tolerance ε is reached .

From the construction setup of the algorithm for the parabolic RB problem we have to assume that the initial data u_0 at $t = 0$ lies in the RB space $\mathbb{V}_{\mathrm{rb}}$. Furthermore, for the algorithm to be computationally efficient, the approximation error $\|u_h(\mu) - u_n(\mu)\|_{\mathbb{V}_h}$ should be an easily estimated by means of *a posteriori* estimator:

$$\|u_h(\mu) - u_n(\mu)\|_{\mathbb{V}_h} \leq \Delta(\mu), \quad \forall \mu \in \mathcal{M}, \tag{1.9}$$

For practical implementation, $\mathcal{M}$ must be replaced by a finite training set Ξ_{train}, and the solution of the optimisation problem (1.8) is reduced to a sorting problem of $\Delta(\mu), \mu \in \Xi_{train}$ to choose the snapshot with the largest *a posteriori* estimator. If the computation of $\Delta(\mu)$ is inexpensive and independent of N_h, Ξ_{train} can be chosen to be large. The algorithm ends when we reach the prescribed accuracy ε: $\max_{\mu \in \Xi_{train}} \Delta_N(\mu) < \varepsilon$.

In the subsequent analysis we shall construct such *a posteriori* estimators for two parabolic problems describing the growth of a glioma tumour in the brain (Chapter 2) and the drug-induced phenotype evolution inside a tumour (Chapter 3). The time-integration schemes are based on a first-order implicit-explicit (IMEX) method (*IMEX-θ method* (1.4)).

Chapter 2

Reduced basis method for a glioma model

2.1 Description of the model

We use the model for glioma growth from [14, p.543ff]

$$\frac{\partial u}{\partial t} = \nabla \cdot \mathbf{J} + \beta(x,t,\mu)u, \quad x \in \Omega \tag{2.1}$$

where $u(x,t)$ denotes the tumour cell density at a position x and time t. The function $\beta(x,t,\mu)$ represents the net rate of growth of cells including proliferation and death (or loss) due to time-varying chemotherapy with dose μ. The diffusional flux of cells, denoted by $\mathbf{J}$, is taken as proportional to the gradient of the cell density, $\mathbf{J} = \alpha(x)\nabla u$. The diffusion coefficient $\alpha(x)$ in all generality takes into account the spatial heterogeneity inside the brain domain Ω (white vs. grey matter, see [14]):

$$\alpha(x) = \begin{cases} d_1, & x \in \Omega_0 \\ d_2, & x \in \Omega \setminus \Omega_0 \end{cases}$$

Equation (2.1) is complemented by Neumann boundary condition on $\partial\Omega$:

$$\mathbf{n} \cdot (\alpha(x)\nabla u) = 0 \tag{2.2}$$

where $\mathbf{n}$ is the unit normal to the boundary $\partial\Omega$ of Ω.

The initial data at $t = 0$ is Gaussian, as in [14] and the net rate of growth σ is exponential in the absence of treatment and independent of x:

$$\beta(x,\mu) = \sigma - \kappa(t)\mu \ .$$

The function $\kappa(t)$ describes the temporal profile of the treatment [14, Eq. (11.52)].

2.2 Variational formulation for the IMEX-θ scheme in the truth space

To solve the problem (2.1) numerically, we use a variational approach, and denote henceforth the finite element approximation space $\mathbb{V}_h$ as the *truth space* [12, 15]. Fix the

value of μ. We assume the solution of (1.4) is approximated by a sequence of functions in $\mathbb{V}_h$, $U_h(\mu) = \{u_h^k(\mu) | k = 0, 1, \dots k_{max}\}$ with sufficient accuracy. Each time layer $u_h^k(\mu)$ is a solution in $\mathbb{V}_h$ obtained from the chosen time integration scheme for time layer $k\tau, k = 0, 1, \dots k_{max}$ with $k_{max}\tau = T_{max}$. This solution is denoted as a *truth solution* or *high fidelity approximation* [12, 15].

Since (2.1) is a pure reaction-diffusion problem with a linear reaction, *first-order in time* schemes are a reasonable choice for computing the *truth solutions* $U_h(\mu)$. The IMEX-θ scheme ($0 \leq \theta \leq 1$) [1, 16] for the equation (2.1) takes the following form:

$$\begin{aligned} \langle u_h^k(\mu), \phi \rangle + \theta\tau \cdot a(u_h^k(\mu), \phi) &= \langle u_h^{k-1}(\mu), \phi \rangle \\ &- (1-\theta)\tau \cdot a(u_h^{k-1}(\mu), \phi) + \langle \beta((k-1)\tau, \mu) u_h^{k-1}(\mu), \phi \rangle, \quad \forall \phi \in \mathbb{V}_h, \end{aligned} \tag{2.3}$$

The bilinear form a in (2.3) is defined as

$$a(u, v) \stackrel{\text{def}}{=} \int_\Omega \alpha(x) \nabla u \cdot \nabla v \, dx \, . \tag{2.4}$$

Due to the inhomogeneous nature of the brain domain (presence of subregions of white or grey matter [14]), the triangulation must be sufficiently refined, which requires very large N_h. However, the solutions of the parabolic problem (2.3) for various parameter values $\mu \in \mathcal{M}$ may lie within a subspace of a lower dimension than N_h.

We seek an approximation of the solutions of the parabolic problem (2.3) for various parameter values $\mu \in \mathcal{M}$ inside a lower-dimensional subspace of $\mathbb{V}_h$ by applying a reduced basis framework. In other words, we aim at approximating the solutions in the truth space by the basis elements $\{\xi_i\}_{i=1}^N$ of a subspace of $\mathbb{V}_h$, which we call a *reduced basis space* $\mathbb{V}_{\text{rb}}^N$, such that the approximation error resulting from the approximation of the truth solution $U_h(\mu)$ by the *reduced basis solution* $U_{\text{rb}}(\mu) \in \mathbb{V}_{\text{rb}}^N$ stays within a prescribed tolerance. Furthermore, we want the computational cost of the reduced basis solution in $\mathbb{V}_{\text{rb}}$ for the different parameter values μ to remain independent of N_h. We refer to the flowchart on Figure 1.2.

2.3 Solving the problem in the reduced basis

Assume that the reduced basis space $V_{\text{rb}}^N \stackrel{\text{def}}{=} \text{span}\{\xi_i\}_{i=1}^N \subset \mathbb{V}_h$ of dimension $N \ll N_h$ has already been found. Let $u_{\text{rb}}^k(\mu)$ be the reduced basis approximation in $\mathbb{V}_{\text{rb}}$ to the truth solution $u_h^k(\mu)$ at time layer $t = k\tau$ for a given μ.

The equality (2.3) implies that the reduced basis solutions $u_{\text{rb}}^k(\mu)$ satisfy

$$\begin{aligned} \langle u_{\text{rb}}^k(\mu), \phi_{\text{rb}} \rangle + \theta\tau \cdot a(u_{\text{rb}}^k(\mu), \phi_{\text{rb}}) &= \langle u_{\text{rb}}^{k-1}(\mu), \phi_{\text{rb}} \rangle \\ &- (1-\theta)\tau \cdot a(u_{\text{rb}}^{k-1}(\mu), \phi_{\text{rb}}) + \langle \beta((k-1)\tau, \mu) u_{\text{rb}}^{k-1}(\mu), \phi \rangle, \quad \forall \phi_{rb} \in \mathbb{V}_{\text{rb}} \, . \end{aligned} \tag{2.5}$$

2.3.1 Algebraic formulation for the time-dependent reduced basis problem

As in [12, Chapter 6.1], we seek the coefficients of the representation of a reduced basis solution $\{u_{\text{rb}}^k(\mu)\} \in \mathbb{V}_{\text{rb}}, 0 \leq k \leq k_{max}$ in the basis $\{\xi_i\}_{i=1}^N$ of $\mathbb{V}_{\text{rb}}$, which satisfies (2.5).

Fix k and let $\{\mathbf{u}_{k,i}^{\mu}\}_{i=1}^{N}$ be the coefficients of the representation of $u_{\mathrm{rb}}^{k}(\mu)$ in the reduced basis $\mathbb{V}_{\mathrm{rb}}$:

$$u_{\mathrm{rb}}^{k}(\mu) = \sum_{i=1}^{N} \mathbf{u}_{k,i}^{\mu} \xi_i \ . \tag{2.6}$$

Then we test (2.5) with all elements in the reduced basis, $\xi_j, 1 \le j \le N$ and we obtain a linear system for $\{\mathbf{u}_{k,i}^{\mu}\}_{i=1}^{N}$ in terms of the coefficients of the representation on the previous $(k-1)$-st time layer, $\{\mathbf{u}_{k-1,i}^{\mu}\}_{i=1}^{N}$:

$$\begin{aligned} \sum_{i=1}^{N} \mathbf{u}_{k,i}^{\mu} \langle \xi_i, \xi_j \rangle + \theta\tau \sum_{i=1}^{N} \mathbf{u}_{k,i}^{\mu} a(\xi_i, \xi_j) &= \sum_{i=1}^{N} \mathbf{u}_{k-1,i}^{\mu} \langle \xi_i, \xi_j \rangle \\ &- \tau \ell^{k-1}(\xi_j; \mu) - (1-\theta)\tau \sum_{i=1}^{N} \mathbf{u}_{k-1,i}^{\mu} a(\xi_i, \xi_j), \quad \forall \xi_j \in \mathbb{V}_{\mathrm{rb}} \ . \end{aligned} \tag{2.7}$$

Here in the right-hand side we let

$$\ell^{k-1}(\xi_j; \mu) \stackrel{\mathsf{def}}{=} p_1^{(k-1)}(\xi_j) - \mu\kappa(t) p_2^{(k-1)}(\xi_j) \ , \tag{2.8}$$

with the individual summands being respectively:

$$p_1^{(k-1)}(\xi_j) = \sigma \sum_{i=1}^{N} \mathbf{u}_{k-1,i}^{\mu} \langle \xi_i, \xi_j \rangle \tag{2.9a}$$

$$p_2^{(k-1)}(\xi_j) = \mu\kappa_{k-1} \sum_{i=1}^{N} \mathbf{u}_{k-1,i}^{\mu} \langle \xi_i, \xi_j \rangle \tag{2.9b}$$

In (2.9b) we denote $\kappa_{k-1} \stackrel{\mathsf{def}}{=} \kappa((k-1)\tau)$.

Using this setup we rewrite the linear problem in matrix notation:

$$(\mathbb{M} + \theta\tau\mathbb{A})\mathbf{u}_k^{\mu} = (\mathbb{M} - (1-\theta)\tau\mathbb{A})\mathbf{u}_{k-1}^{\mu} - \tau L_{k-1}^{\mu} \mathbf{u}_{k-1}^{\mu} \tag{2.10}$$

where

$$L_{k-1}^{\mu} = \mathbb{P}_1 - \mu\mathbb{P}_2^{(k-1)} \ . \tag{2.11}$$

and $\mathbb{M}, \mathbb{A}, \mathbb{P}_1, \mathbb{P}_2^{(k-1)}$ are matrices that can be computed and stored during the *offline stage* because they are independent of μ. They are defined in the following manner:

$$\begin{aligned} &\mathbb{M} : (\mathbb{M})_{ij} \stackrel{\mathsf{def}}{=} \langle \xi_i, \xi_j \rangle, \\ &\mathbb{A} : (\mathbb{A})_{ij} \stackrel{\mathsf{def}}{=} a(\xi_i, \xi_j), \\ &\mathbb{P}_1 \stackrel{\mathsf{def}}{=} \sigma\mathbb{M}, \quad \mathbb{P}_2^{(k-1)} \stackrel{\mathsf{def}}{=} \kappa_{k-1}\mathbb{M} \ . \end{aligned}$$

Finally, the solution resulting in the reduced basis approximation is recovered from $\mathbf{u}_k^{\mu}$ via the RB matrix $\mathbb{V} = [\xi_i]$, via the relation $U_{\mathrm{rb}}(\mu) = \{u_{\mathrm{rb}}^{k}(\mu)\}, u_{\mathrm{rb}}^{k}(\mu) \stackrel{\mathsf{def}}{=} \mathbb{V}\mathbf{u}_k^{\mu}$.

2.3.2 A posteriori error analysis for the IMEX-θ scheme

Our goal is use a carefully chosen sequence of snapshots $\{u_h^k(\mu)|k = 0, 1, \dots k_{max}, \mu \in \Xi'_{train}\}$ to find a reduced basis that can approximate well the solution for all $\mu \in \mathcal{M}$, that is, to keep the approximation error

$$\|u_h(\mu) - u_{\mathrm{rb}}(\mu)\|_{\mathbb{V}_h}$$

below a given error threshold.

The construction of the reduced basis from the snapshots will be performed during the *offline phase* via the POD-greedy algorithm. The choice of points in the parameter training set Ξ_{train} shall be assumed by some appropriate sampling procedure. We shall use a greedy algorithm with a posteriori error estimates approximation error between the truth solution (2.3) and the reduced basis solution (2.5). These estimates will be derived in a later section. The computation of the approximated particular solution $U_h(\mu)$ for a given μ is done in the *online phase* and based on the computation of its coefficients in the reduced basis expansion explained in the Section 2.3.1

In order to construct an efficient error estimate for use inside the POD-greedy algorithm that successively refines the reduced basis with new elements, we have to be able to estimate how the approximation error changes by adding an additional element to the basis. This is done by *a posteriori* error analysis rooted in carefully chosen residuals whose computation can be made in an efficient manner.

Here we shall derive a general estimate for the approximation error based on the IMEX-θ scheme for a parametrised semilinear reaction-diffusion problem of the form:

$$\partial_t u - \alpha(\mu)\Delta u = f(u;\mu), \quad u \in H^1(\Omega), t \in (0, T_{max}) \tag{2.12}$$

with parameter $\mu \in \mathcal{M}$. In addition let $f(\cdot;\mu)$ be Lipschitz continuous:

$$|f(z;\mu) - f(z';\mu)| \leq \ell_f(\mu)|z - z'|, \quad \sup_\mu \ell_f(\mu) = \ell_{sup}, \tag{2.13}$$

with u subject to a given initial datum u_0 and Neumann boundary conditions on $\partial\Omega$. We remark that the model (2.1) is a special case of such a semilinear parabolic problem.

The IMEX-θ scheme ($0 \leq \theta \leq 1$) for the truth solution of(2.12) in a finite element approximation space $\mathbb{V}_h \subset H^1(\Omega)$ for a fixed μ writes as

$$\begin{aligned}\langle u_h^{k+1}(\mu) - u_h^k(\mu), \phi\rangle + \tau a(\theta u_h^{k+1}(\mu) \\ + (1-\theta)u_h^k(\mu), \phi;\mu) = \tau\langle f(u_h^k(\mu);\mu), \phi\rangle, \quad \forall\phi \in \mathbb{V}_h.\end{aligned} \tag{2.14}$$

where the bilinear form is defined as

$$a(u, v;\mu) \stackrel{\mathsf{def}}{=} \int_\Omega \alpha(\mu)\nabla u \cdot \nabla v \; dx \; . \tag{2.15}$$

Assume that $a(\cdot,\cdot;\mu)$ fulfils the following criteria which determine its coercivity and continuity:

$$\begin{aligned} a_{min}\|u\|^2_{H^1} \leq |a(u,u;\mu)|, \quad \forall u \in H^1(\Omega) \text{ with } a_{min} \stackrel{\mathsf{def}}{=} \inf_\mu \alpha(\mu) \\ |a(u,v)| \leq a_{max}\|u\|_{H^1}\|v\|_{H^1} \text{ with } a_{max} \stackrel{\mathsf{def}}{=} \sup_\mu \alpha(\mu) \; . \end{aligned} \tag{2.16}$$

By assumption the coercivity and continuity constants satisfy $0 < a_{min} \leq a_{min} < \infty$.

Define the *approximation error* between the truth and the reduced basis solution at time layer $k\tau$ as $e_k \stackrel{\text{def}}{=} u_h^k - u_{\text{rb}}^k \in \mathbb{V}_h$. Using (2.14) we work towards an evolution equation for the error:

$$\begin{aligned}
&\frac{1}{\tau}\langle e_{k+1} - e_k, \phi\rangle + a(\theta e_{k+1} + (1-\theta)e_k, \phi; \mu) \\
&\quad = \langle f(u_h^k), \phi\rangle - \frac{1}{\tau}\langle u_{\text{rb}}^{k+1}, \phi\rangle - \theta a(u_{\text{rb}}^{k+1}, \phi; \mu) + \frac{1}{\tau}\langle u_{\text{rb}}^k, \phi\rangle - (1-\theta)a(u_{\text{rb}}^k, \phi; \mu) \\
&\qquad = \langle f(u_h^k) - f(u_{\text{rb}}^k), \phi\rangle - \frac{1}{\tau}\langle u_{\text{rb}}^{k+1} - u_{\text{rb}}^k, \phi\rangle \\
&\qquad\quad - a(\theta u_{\text{rb}}^{k+1} + (1-\theta)u_{\text{rb}}^k, \phi; \mu) + \langle f(u_{\text{rb}}^k), \phi\rangle, \quad \forall \phi \in \mathbb{V}_h \ .
\end{aligned}$$

Denote the residual of the reduced basis solution u_{rb} on time-layer $k+1$ by

$$r^{k+1}(\phi; \mu) = \langle f(u_{\text{rb}}^k), \phi\rangle - \frac{1}{\tau}\langle u_{\text{rb}}^{k+1} - u_{\text{rb}}^k, \phi\rangle - a(\theta u_{\text{rb}}^{k+1} + (1-\theta)u_{\text{rb}}^k, \phi; \mu), \quad \forall \phi \in \mathbb{V}_h. \tag{2.17}$$

Using the residual we have the following evolution equation for the error e_{k+1}:

$$\begin{aligned}
&\frac{1}{\tau}\langle e_{k+1} - e_k, \phi\rangle + a(\theta e_{k+1} + (1-\theta)e_k, \phi; \mu) \\
&\qquad = \langle f(u_h^k) - f(u_{\text{rb}}^k), \phi\rangle + r^{k+1}(\phi; \mu), \quad \forall \phi \in \mathbb{V}_h \ .
\end{aligned} \tag{2.18}$$

We seek *a posteriori* error estimates for the error e_k based on the residual (2.17). We define the norm of the residual r^{k+1} in the dual space $\mathbb{V}_h'$ as

$$\|r^{k+1}(\cdot; \mu)\|_* \stackrel{\text{def}}{=} \sup_{\phi \in \mathbb{V}_h} \frac{|r^{k+1}(\phi; \mu)|}{\|\phi\|_{H^1}} \ . \tag{2.19}$$

Note that the H^1-norm and the L^2-norms are equivalent on the finite-dimensional finite element approximation space $\mathbb{V}_h$. Since r^{k+1} is a linear functional on $\mathbb{V}_h \subset H^1(\Omega)$, by the Riesz representation theorem, there exists a unique $\tilde{r}^{k+1} \in \mathbb{V}_h$ such that

$$\langle \tilde{r}^{k+1}(\mu), \phi\rangle_{H^1} = r^{k+1}(\phi; \mu), \quad \forall \phi \in \mathbb{V}_h \tag{2.20}$$

and $\|r^{k+1}(\cdot; \mu)\|_* = \|\tilde{r}^{k+1}(\mu)\|_{H^1}$.

Note that whenever r^{k+1} has an affine dependence on μ, the norm of the residual can be efficiently computed. We shall factor the residual into easily-computable summands using the affine dependence in the next section.

We proceed following [16] to obtain estimates of the approximation error e_k.

Proposition 1. *Suppose that f is a Lipschitz-continuous function with Lipschitz constant ℓ_{sup} (2.13). Let $r^k(\cdot; \mu)$ be the residual from (2.17), with norm $\|r^k(\mu)\|_*$ defined in (2.19). Then we have the following estimates for the approximation error $e_k(\mu) = u_h^k(\mu) - u_{\text{rb}}^k(\mu)$ between the truth and the reduced basis solution in the IMEX-θ scheme.*

(i) Let $\theta \geq 1/2$. Then

$$\|e_k(\mu)\|_{L^2}^2 \leq \frac{\tau}{a_{min}} \sum_{i=1}^{k} (1 + \tau \frac{\ell_{sup}^2}{a_{min}})^{k-i} \|r^i(\mu)\|_*^2 \ . \tag{2.21}$$

(ii) Let $\theta < 1/2$. Assume the time step τ and the domain triangulation $\mathcal{T}_h$ satisfy

$$\tau\left(1+\frac{c_\Omega}{h^2}\right) < \frac{2a_{min}}{(1-2\theta)a_{max}^2}\,. \tag{2.22}$$

Then

$$\|e_k(\mu)\|_{L^2}^2 \le 2\tau C_{\epsilon,\eta}\sum_{i=1}^{k}(1+2\tau\ell_{sup}^2 C_{\epsilon,\eta})^{k-i}\|r^i(\mu)\|_*^2\,, \tag{2.23}$$

for an appropriately chosen constant $C_{\epsilon,\eta}$ which is independent of μ, τ, h.

Proof. Testing (2.18) with $\phi = \theta e_{k+1}+(1-\theta)e_k$ and doing some algebraic transformations we have for the left-hand size of (2.18):

$$\begin{aligned}
\frac{1}{\tau}\langle e_{k+1}-e_k, \theta e_{k+1}+(1-\theta)e_k\rangle &+ a(\theta e_{k+1}+(1-\theta)e_k, \theta e_{k+1}+(1-\theta)e_k;\mu)\\
&= \frac{1}{2\tau}\|e_{k+1}\|_{L^2}^2 - \frac{1}{2\tau}\|e_k\|_{L^2}^2 + \frac{1}{\tau}\left(\theta-\frac{1}{2}\right)\|e_{k+1}-e_k\|_{L^2}^2\\
&\quad + a(\theta e_{k+1}+(1-\theta)e_k, \theta e_{k+1}+(1-\theta)e_k;\mu)\\
&\ge \frac{1}{2\tau}\|e_{k+1}\|_{L^2}^2 - \frac{1}{2\tau}\|e_k\|_{L^2}^2 + \frac{1}{\tau}\left(\theta-\frac{1}{2}\right)\|e_{k+1}-e_k\|_{L^2}^2\\
&\quad + a_{min}\|\theta e_{k+1}+(1-\theta)e_k\|_{H^1}^2,
\end{aligned}$$

with the last inequality due to the coercivity of the bilinear form a.

Using the Lipschitz continuity of f given by (2.13), Hölder's inequality, and the embedding $H^1(\Omega)\subset L^2(\Omega)$ in this order we obtain:

$$\begin{aligned}
\langle f(u_h^k)-f(u_{\rm rb}^k),\phi\rangle &\le \int_\Omega |f(u_h^k)-f(u_{\rm rb}^k)||\phi|\,dx\\
&\le \ell_{sup}\|\underbrace{u_h^k-u_{\rm rb}^k}_{e_k}\|_{L^2}\|\phi\|_{L^2} \le \ell_{sup}\|e_k\|_{L^2}\|\phi\|_{H^1},
\end{aligned} \tag{2.24}$$

Hence, the right-hand side of (2.18) when $\phi = \theta e_{k+1}+(1-\theta)e_k$ can be bounded by

$$\begin{aligned}
\langle f(u_h^k)-f(u_{\rm rb}^k), \theta e_{k+1}+(1-\theta)e_k\rangle &+ r^{k+1}(\theta e_{k+1}+(1-\theta)e_k;\mu)\\
&\le (\ell_{sup}\|e_k\|_{L^2}+\|r^{k+1}(\mu)\|_*)\cdot\|\theta e_{k+1}+(1-\theta)e_k\|_{H_1}\,.
\end{aligned}$$

Using next Young's inequality, for all $0<\epsilon\le 1$, we have

$$\begin{aligned}
&(\ell_{sup}\|e_k\|_{L^2}+\|r^{k+1}(\mu)\|_*)\cdot\|\theta e_{k+1}+(1-\theta)e_k\|_{H_1}\\
&\quad\le \frac{1}{4\epsilon a_{min}}((\ell_{sup}\|e_k\|_{L^2}+\|r^{k+1}(\mu)\|_*))^2 + \epsilon a_{min}\|\theta e_{k+1}+(1-\theta)e_k\|_{H_1}^2\\
&\quad\le \frac{1}{2\epsilon a_{min}}(\ell_{sup}^2\|e_k\|_{L^2}^2+\|r^{k+1}(\mu)\|_*^2) + \epsilon a_{min}\|\theta e_{k+1}+(1-\theta)e_k\|_{H_1}^2\,.
\end{aligned}$$

Combining these estimates we see that

$$\frac{1}{2\tau}\|e_{k+1}\|_{L^2}^2 - \frac{1}{2\tau}\|e_k\|_{L^2}^2 + \frac{1}{\tau}\left(\theta - \frac{1}{2}\right)\|e_{k+1}-e_k\|_{L^2}^2 + a_{min}\|\theta e_{k+1} + (1-\theta)e_k\|_{H^1}^2$$
$$\leq \frac{1}{2\epsilon a_{min}}(\ell_{sup}^2\|e_k\|_{L^2}^2 + \|r^{k+1}(\mu)\|_*^2) + \epsilon a_{min}\|\theta e_{k+1} + (1-\theta)e_k\|_{H_1}^2, \tag{2.25}$$

for all $0 < \epsilon \leq 1$.

Now we consider two cases to continue the estimation of the approximation error. Consider at first the case $\theta \geq \frac{1}{2}$. Then

$$\left(\theta - \frac{1}{2}\right)\|e_{k+1}-e_k\|_{L^2}^2 + (1-\epsilon)a_{min}\|\theta e_{k+1} + (1-\theta)e_k\|_{H_1}^2 \geq 0$$

and we may set $\epsilon = 1$ in (2.25). After multiplying by 2 both sides of (2.25) and rearranging, we obtain:

$$\frac{1}{\tau}\|e_{k+1}\|_{\ell_{sup}^2}^2 - \left(\frac{1}{\tau} + \frac{\ell_{sup}^2}{a_{min}}\right)\|e_k\|_{L^2}^2 \leq \frac{1}{a_{min}}\|r^{k+1}(\mu)\|_*^2, \text{ so}$$
$$\|e_{k+1}\|_{L^2}^2 - \left(1 + \frac{\tau\ell_{sup}^2}{a_{min}}\right)\|e_k\|_{L^2}^2 \leq \frac{\tau}{a_{min}}\|r^{k+1}(\mu)\|_*^2 .$$

Consider next the case $\theta < \frac{1}{2}$. From the assumption (2.22) we conclude that $1 + \frac{\tau}{h^2}$ is bounded by some constant independent of τ, h. Testing (2.18) with $\phi = e_{k+1} - e_k$ we have

$$\begin{aligned}\frac{1}{\tau}\|e_{k+1}-e_k\|_{L^2}^2 &= -a(\theta e_{k+1} + (1-\theta)e_k, e_{k+1}-e_k;\mu)\\ &\quad + \langle f(u_h^k) - f(u_{\text{rb}}^k), e_{k+1}-e_k\rangle + r^{k+1}(e_{k+1}-e_k;\mu)\\ &\leq a_{max}\|\theta e_{k+1} + (1-\theta)e_k\|_{H^1}\cdot\|e_{k+1}-e_k\|_{H^1}\\ &\quad + (\ell_{sup}\|e_k\|_{L^2} + \|r^{k+1}(\mu)\|_*)\cdot\|e_{k+1}-e_k\|_{H_1} .\end{aligned} \tag{2.26}$$

The inverse inequality (1.1) applied to $e_{k+1} - e_k$ gives us the estimate

$$\|e_{k+1}-e_k\|_{H_1} \leq \sqrt{1 + \frac{c}{h^2}}\|e_{k+1}-e_k\|_{L^2}. \tag{2.27}$$

Therefore, plugging (2.27) into (2.26) gives

$$\frac{1}{\tau}\|e_{k+1}-e_k\|_{L^2} \leq \sqrt{1+\frac{c}{h^2}}\left(a_{max}\|\theta e_{k+1} + (1-\theta)e_k\|_{H^1} + \ell_{sup}\|e_k\|_{L^2} + \|r^{k+1}(\mu)\|_*\right)$$

Choose $\eta, \epsilon > 0$ small enough so that the constant

$$\kappa_\eta = 2(1-\epsilon)a_{min} - (1-2\theta)a_{max}(a_{max}+\eta)\tau\left(1 + \frac{c}{h^2}\right) \tag{2.28}$$

is positive. Then rearranging (2.25) we see that

$$\begin{aligned}
&\frac{1}{2\tau}\|e_{k+1}\|_{L^2}^2 - \frac{1}{2\tau}\|e_k\|_{L^2}^2 + a_{min}(1-\epsilon)\|\theta e_{k+1} + (1-\theta)e_k\|_{H^1}^2 \\
&\qquad \le \frac{1}{2\epsilon a_{min}}(\ell_{sup}^2\|e_k\|_{L^2}^2 + \|r^{k+1}(\mu)\|_*^2) + \frac{1}{\tau}\left(\frac{1}{2}-\theta\right)\|e_{k+1}-e_k\|_{L^2}^2 \\
&\qquad\quad \le \frac{1}{2\epsilon a_{min}}(\ell_{sup}^2\|e_k\|_{L^2}^2 + \|r^{k+1}(\mu)\|_*^2) + \left(\frac{1}{2}-\theta\right)\tau\left(1+\frac{c}{h^2}\right) \\
&\qquad\qquad \times \left(a_{max}\|\theta e_{k+1} + (1-\theta)e_k\|_{H^1} + \ell_{sup}\|e_k\|_{L^2} + \|r^{k+1}(\mu)\|_*\right)^2 . \quad (2.29)
\end{aligned}$$

Applying the inequality

$$(a_{max}x + y)^2 \le a_{max}^2x^2 + y^2 + a_{max}(\eta x^2 + \frac{y^2}{\eta}) = a_{max}(a_{max}+\eta)x^2 + (1+\frac{a_{max}}{\eta})y^2$$

with

$$x = \|\theta e_{k+1} + (1-\theta)e_k\|_{H^1}, \quad y = \ell_{sup}\|e_k\|_{L^2} + \|r^{k+1}(\mu)\|_*,$$

to the last term in (2.29) and rearranging we see that

$$\begin{aligned}
&\frac{1}{2\tau}\|e_{k+1}\|_{L^2}^2 - \frac{1}{2\tau}\|e_k\|_{L^2}^2 + \frac{\kappa_\eta}{2}\|\theta e_{k+1} + (1-\theta)e_k\|_{H^1}^2 \\
&\qquad\qquad \le \frac{1}{2\epsilon a_{min}}(\ell_{sup}^2\|e_k\|_{L^2}^2 + \|r^{k+1}(\mu)\|_*^2) \\
&\qquad + \left(\frac{1}{2}-\theta\right)\tau\left(1+\frac{c_\Omega}{h^2}\right)(1+\frac{a_{max}}{\eta})(\ell_{sup}\|e_k\|_{L^2} + \|r^{k+1}(\mu)\|_*)^2 \\
&\qquad \le \underbrace{\left(\frac{1}{2\epsilon a_{min}} + (1-2\theta)\tau\left(1+\frac{c_\Omega}{h^2}\right)(1+\frac{a_{max}}{\eta})\right)}_{\le C_{\epsilon,\eta}}(\ell_{sup}^2\|e_k\|_{L^2}^2 + \|r^{k+1}(\mu)\|_*^2) .
\end{aligned}$$

where $C_{\epsilon,\eta}$ is independent of h, τ. We use the positivity of κ_η to obtain thus:

$$\begin{aligned}
\frac{1}{2\tau}\|e_{k+1}\|_{L^2}^2 - \frac{1}{2\tau}\|e_k\|_{L^2}^2 &\le C_{\epsilon,\eta}(\ell_{sup}^2\|e_k\|_{L^2}^2 + \|r^{k+1}(\mu)\|_*^2), \text{ so} \\
\|e_{k+1}\|_{L^2}^2 - (1+2\tau\ell_{sup}^2C_{\epsilon,\eta})\|e_k\|_{L^2}^2 &\le 2\tau C_{\epsilon,\eta}\|r^{k+1}(\mu)\|_*^2 .
\end{aligned}$$

Now we combine the results from both cases to obtain the error estimator. Using Lemma 1 and the fact that the high-fidelity solution and the RB solution share the same initial data $u_h^0 = u_{\text{rb}}^0$, $e_0 \equiv 0$ by construction of the reduced basis, so we arrive to

$$\|e_k\|_{L^2}^2 \le 2\tau C_{\epsilon,\eta}\sum_{i=1}^{k}(1+2\tau\ell_{sup}^2C_{\epsilon,\eta})^{k-i}\|r^i(\mu)\|_*^2 .$$

Doing these recursive computations we arrive to the statement of the Proposition. □

Lemma 1. *Let $b > 0$ and $\{x_i\}, \{r_i\}$ be non-negative squences which satisfy*

$$x_{i+1} - bx_i \le r_{i+1}, \quad \forall i \in \mathbb{N} .$$

Then

$$x_k \le b^kx_0 + b^{k-1}r_1 + b^{k-2}r_2 + \ldots + br_{k-1} + r_k, \quad \forall k \in \mathbb{N} .$$

Proof. By telescopic sum and induction. □

2.3.3 Computing the a posteriori error estimator

Proposition 1 provides an a posteriori error estimator for the approximation error $e_k(\mu)$ between the truth solution (2.3) and the reduced basis solution (2.5) at time layer $k\tau$ of the form

$$\|e_k(\mu)\|_{L^2}^2 \leq \Delta_k(\mu) = \tau C_1 \sum_{i=1}^{k} C_2^{k-i} \|r^i(\mu)\|_*^2 \tag{2.30}$$

with $C_1 > 0, C_2 > 1$. By virtue of (2.30), for a given solution trajectory $U_h(\mu)$, the quantity $\Delta(\mu)$ attains its maximum at $k = k_{max}$ [9]. Hence it suffices to set as the *a posteriori* error estimator for the scheme (2.5):

$$\Delta_k(\mu) \stackrel{\text{def}}{=} \Delta_{k_{max}}(\mu) \ .$$

It remains to describe an efficient manner to compute $\Delta(\mu)$. Recall the norm of the residual r^k given by (2.17), which is $\|r^k(\mu)\|_* = \|\tilde{r}^k(\mu)\|_{H^1}$. We now use the affine dependence of the reaction term for the concrete problem (glioma model) given in (2.1) to decompose the norm of the residual into summands that are computed efficiently during the online stage. Using the RB expansion of u_{rb}^k, given in (2.6), we rewrite the residual as

$$\begin{aligned} r^{k+1}(\phi;\mu) &= \langle f(u_{\text{rb}}^k), \phi\rangle - \frac{1}{\tau}\langle u_{\text{rb}}^{k+1} - u_{\text{rb}}^k, \phi\rangle - a(\theta u_{\text{rb}}^{k+1} + (1-\theta)u_{\text{rb}}^k, \phi) \\ &= \sigma \sum_{i=1}^{N} \mathbf{u}_{k,i}^{\mu} \langle \xi_i, \phi\rangle - \mu\kappa_k \sum_{i=1}^{N} \mathbf{u}_{k,i}^{\mu} \langle \xi_i, \phi\rangle - \frac{1}{\tau}\sum_{i=1}^{N} (\mathbf{u}_{k+1,i}^{\mu} - \mathbf{u}_{k,i}^{\mu})\langle \xi_i, \phi\rangle \\ &\qquad - \sum_{i=1}^{N} (\theta \mathbf{u}_{k+1,i}^{\mu} + (1-\theta)\mathbf{u}_{k,i}^{\mu}) a(\xi_i, \phi), \quad \forall \phi \in \mathbb{V}_h \ . \end{aligned} \tag{2.31}$$

Following [12] we introduce the coefficient vector $\mathbf{r}^k(\mu) \in \mathbb{R}^{4N}$

$$\mathbf{r}^k(\mu) \stackrel{\text{def}}{=} (\sigma \mathbf{u}_{k,i}^{\mu}, -\mu\kappa_k \mathbf{u}_{k,i}^{\mu}, -\tfrac{1}{\tau}(\mathbf{u}_{k+1,i}^{\mu} - \mathbf{u}_{k,i}^{\mu}), (\theta \mathbf{u}_{k+1,i}^{\mu} + (1-\theta)\mathbf{u}_{k,i}^{\mu}))^T$$

and the vector of forms $\mathfrak{R} \in (\mathbb{V}'_{\text{rb}})^{4N}$

$$\mathfrak{R} \stackrel{\text{def}}{=} (\{\langle \xi_i, \cdot\rangle\}_{i=1}^N, \{\langle \xi_i, \cdot\rangle\}_{i=1}^N, \{\langle \xi_i, \cdot\rangle\}_{i=1}^N, \{a(\xi_i, \cdot)\}_{i=1}^N) \ ,$$

leading to the following representation of the residual $r^{k+1}(\phi;\mu)$:

$$r^{k+1}(\phi;\mu) = \sum_{j=1}^{4N} \mathbf{r}_j^k(\mu)\mathfrak{R}_j(\phi), \quad \forall \phi \in \mathbb{V}_{rb} \ . \tag{2.32}$$

Let $\hat{r}_j$ denote the Riesz representation of $\mathfrak{R}_j$ so that $\langle \hat{r}_j, \phi\rangle_{H^1} = \mathfrak{R}_j(\phi), \forall j$ (which is independent of the time layer k). We obtain the following relation for the Riesz representation of r^{k+1} and its norm

$$\tilde{r}^{k+1}(\mu) = \sum_{j=1}^{4N} \mathbf{r}_j^k(\mu)\hat{r}_j \Rightarrow \|\tilde{r}^{k+1}(\mu)\|_{H^1}^2 = \sum_{j=1}^{4N}\sum_{j'=1}^{4N} \mathbf{r}_j^k(\mu)\mathbf{r}_{j'}^k(\mu)\langle \hat{r}_j, \hat{r}_{j'}\rangle_{H_1} \ .$$

The computation of the inner products $\langle \hat{r}_j, \hat{r}_{j'} \rangle_{H_1}$ can be done once during the offline stage, because they are independent of μ. To find $\hat{r}_j$, we use its expansion in the basis functions φ_ℓ of the truth space $\mathbb{V}_h$, and note that for all j, ℓ we have

$$\hat{r}_j = \sum_{\ell=1}^{N} \langle \hat{r}_j, \varphi_\ell \rangle \tilde{\varphi}_\ell = \sum_{\ell=1}^{N} \mathfrak{R}_j(\varphi_\ell) \tilde{\varphi}_\ell,$$

with $\{\tilde{\varphi}_\ell\}_{\ell=1}^N$ being the dual (or biorthogonal basis) associated to $\{\varphi_\ell\}_{\ell=1}^N$ [4]. $\mathfrak{R}_j(\varphi_\ell)$ is directly computable during the offline stage, and we define the matrix $\mathbf{R} \in \mathbb{R}^{N \times 4N}$ as follows : $\mathbf{R}_{\ell j} \overset{\text{def}}{=} \mathfrak{R}_j(\varphi_\ell)$. Therefore, we may compute the inner products $\langle \hat{r}_j, \hat{r}_{j'} \rangle_{H_1}$ by using the Gram matrix representation of the dual basis, which is $\mathbb{G}^{-1}$, where the Gram matrix $\mathbb{G} \in \mathbb{R}^{N \times N}$ is defined as $(\mathbb{G})_{ij} = \langle \varphi_j, \varphi_i \rangle$:

$$\langle \hat{r}_j, \hat{r}_{j'} \rangle_{H_1} = (\mathbf{R}^T \mathbb{G}^{-1} \mathbf{R})_{j'j} \Rightarrow \|\tilde{r}^{k+1}(\mu)\|_{H^1}^2 = \mathbf{r}^k(\mu)^T \mathbf{R}^T \mathbb{G}^{-1} \mathbf{R} \mathbf{r}^k(\mu) \ .$$

We refer to [15, p. 54ff] for the technical details involving the algebraic computation of $\mathbf{R}_{j\ell}$ using a change of basis matrix to the basis $\{\varphi_i\}_{i=1}^{N_h}$ of the truth space $\mathbb{V}_h$.

Chapter 3

Reduced basis method for a selection-mutation model

3.1 Description of the model

We consider the model of phenotype evolution for a cancer cell population proposed in [3]. The cell population is structured in the phenotype space $\Omega = [0,1]^2$, where the cell density $u(x,y,t) \geq 0$ models the density of cells with normalised level x of survival potential and normalised level y of proliferative potential at time $t \in [0, T_{max}]$.

The global density of the cancer cell population at time t is given as

$$\rho(t) = \int_\Omega u(x,y,t)\ dxdy. \tag{3.1}$$

The time evolution of the structured cell population under stress-induced adaptation during chemotherapy is given by an integro-differential parabolic problem:

$$\frac{\partial u}{\partial t} + \frac{\partial}{\partial y}\left(\mathbf{v}(x,\mu,t)u\right) = F(x,y,u,\mu)u + \alpha\Delta u \tag{3.2}$$

where the diffusion term $\alpha\Delta u$ represents the non-genetic instability, driven by random fluctuations in phenotype at average rate $\alpha > 0$, the advection term with velocity $\mathbf{v}(x,\mu,t)$ models the effect of stress-induced adaptation of the cell proliferative potential, dependent on the drug concentration μ, and the effect of selection F [3, Suppl. Material].

The functional forms of $\mathbf{v}, F$ in [3] are given by

$$\begin{aligned} \mathbf{v}(x,\mu,t) &= -v\mu(t)\mathfrak{h}(x-x^*), \quad v \geq 0, 0 < x^* < 1 \\ F(x,y,u,\mu) &= \beta(x,y)(1-\rho(t)) - \gamma(x,\mu) \end{aligned}$$

where x^* is a fixed number in $(0,1)$, β is the proliferation rate and γ is the death rate. $\mathfrak{h}(z)$ denotes the Heaviside function:

$$\mathfrak{h}(z) = \begin{cases} 1, & z \geq 0, \\ 0, & z < 0 \end{cases}$$

The growth law F takes into account the crowding effects in the tumour: when the cell density ρ increases, the growth rate F decreases.

In this section we consider a special case of the model (3.2) inspired by the work of [13]. We consider only mutation and selection in a population with phenotype structure (so $\mathbf{v} \equiv 0$ for all $t > 0$) and include the action of a cytotoxic drug that increases the removal rate γ. Neumann boundary conditions for (3.3) are imposed as in [13]. The model equations read:

$$\begin{aligned} \frac{\partial u}{\partial t} &= F(x, y, u, \mu) + \alpha \Delta u \quad \text{ on } \Omega = [0,1]^2 \\ F(x, y, u, \mu) &= (\beta(x, y) - \rho(t) - \gamma(x, y)\mu)u \\ \rho(t) &= \int_\Omega u(x, y, t) dxdy \\ \frac{\partial u}{\partial \nu} &= 0 \quad \text{ on } \partial\Omega \end{aligned} \tag{3.3}$$

Such models admit a unique globally stable solution [13].

We use the functional form of β, γ proposed by the authors of [3] in the model (3.3):

$$\beta(x, y) = (a_1 + a_2 y + a_3(1 - x)) - b_3 \,, \tag{3.4a}$$

$$\gamma(x, y) = \mu(b_1 + b_2(1 - x)) \,. \tag{3.4b}$$

Here $\mu \in \mathcal{M} = [0, \mu_{max}]$ is the range of the applicable drug dose in the chemotherapy, and we see the death term's affine dependence on the drug dose parameter μ.

In order to descrtibe the offline and online stages of the reduced basis method for solving (3.3), we have to recall the following preliminaries.

3.2 Variational formulation for the IMEX-θ scheme in the truth space

We set as the *truth space* a finite element approximation space $\mathbb{V}_h$ of dimension N_h. Fix the value of μ. We assume the solution $u(t_k, \cdot)$ of (3.3) at time layers $t_k = k\tau, k = 0, 1, \dots k_{max}$ with $k_{max}\tau = T_{max}$ is approximated by a sequence $\{u_h^k(\mu) | k = 0, 1, \dots N\}$ with sufficient accuracy. Each $u_h^k(\mu)$ is obtained by the chosen time-integration scheme.

Unlike the glioma model presented in Chapter 2, the variational formulation of model (3.3) consists of a stiff-term (the numerical Laplacian) and an integral term (the integral $\rho(t) = \int_\Omega u(x, y, t)\ dxdy$), that cannot be solved for numerically at each time layer. Hence, we must resort to an IMEX scheme for the time integration. Due to (3.3) being a reaction-diffusion system with a low order non-linearity (it is *quasi-linear* in a sense), it is sufficient to use a first-order scheme as long as we use finite element spaces of higher order to increase the accuracy in the approximation of the integral term $\rho(t)$.

The scheme (1.4) is rewritten as

$$\begin{aligned} \langle u_h^k(\mu), \phi \rangle + \theta\tau \cdot a(u_h^k(\mu), \phi; \mu) &= \langle u_h^{k-1}(\mu), \phi \rangle \\ - (1 - \theta)\tau \cdot a(u_h^{k-1}(\mu), \phi; \mu) &+ (F(u_h^{k-1}(\mu)), \phi; \mu), \quad \forall \phi \in \mathbb{V}_h, \end{aligned} \tag{3.5}$$

with the last term on the right-hand side defined as

$$
\begin{aligned}
(F(u_h^{k-1}(\mu)),\phi;\mu) &\stackrel{\text{def}}{=} \tau p_1^{(k-1)}(\phi;\mu) - \mu\tau p_2^{(k-1)}(\phi;\mu) - \tau p_3^{(k-1)}(\phi;\mu)\\
p_1^{(k-1)}(\phi;\mu) &= \langle u_h^{k-1}(\mu)\beta(\cdot),\phi\rangle\\
p_2^{(k-1)}(\phi;\mu) &= \langle u_h^{k-1}(\mu)\gamma(\cdot),\phi\rangle\\
p_3^{(k-1)}(\phi;\mu) &= \rho_k\langle u_h^{k-1}(\mu),\phi\rangle \quad \text{with} \quad \rho_{k-1} = \int_\Omega u_h^{k-1}(\mu)\, dxdy,
\end{aligned}
\tag{3.6}
$$

for a given parameter value μ.

We seek an approximation of the solutions of the evolution problem (3.5) for various parameter values $\mu \in \mathcal{M}$ inside a subspace of $\mathbb{V}_h$ of much lower dimension. As for the glioma model, we aim at approximating the solutions in the truth space by the basis elements $\{\xi_i\}_{i=1}^N$ of a subspace of $\mathbb{V}_h$, which we call a *reduced basis space* $\mathbb{V}_{\text{rb}}^N$, such that the approximation error resulting from the approximation of the truth solution $U_h(\mu)$ by the *reduced basis solution* $U_{\text{rb}}(\mu) \in \mathbb{V}_{\text{rb}}^N$ stays within a prescribed tolerance. Furthermore, we want the computational cost of the reduced basis solution in $\mathbb{V}_{\text{rb}}^N$ to remain independent of N_h for the different parameter values μ.

3.3 Solving the problem in the reduced basis space

Our analysis of the RB solution begins with the variational formulation. We denote a reduced basis space $\mathbb{V}_{\text{rb}}^N \stackrel{\text{def}}{=} \text{span}\{\xi_i\}_{i=1}^N \subset \mathbb{V}_h$ of dimension $N \ll N_h$. Let $u_{\text{rb}}^k(\mu)$ be the reduced basis approximation in $\mathbb{V}_{\text{rb}}^N$ to the truth solution $u_h^k(\mu)$ at the time layer $k\tau$ for a given μ. The equality (3.5) implies that the reduced basis solution $u_{\text{rb}}^k(\mu)$ satisfies

$$
\begin{aligned}
\langle u_{\text{rb}}^k(\mu),\phi\rangle + \theta\tau\cdot a(u_{\text{rb}}^k(\mu),\phi;\mu) &= \langle u_{\text{rb}}^{k-1}(\mu),\phi\rangle\\
&- (1-\theta)\tau\cdot a(u_{\text{rb}}^{k-1}(\mu),\phi;\mu) + (F(u_{\text{rb}}^{k-1}(\mu)),\phi;\mu), \quad \forall\phi\in\mathbb{V}_{\text{rb}}\ .
\end{aligned}
\tag{3.7}
$$

3.3.1 Algebraic formulation for the time-dependent reduced basis problem

As in [12, Chapter 6.1], we seek the coefficients of the basis expansion of the reduced basis solution $\{u_{\text{rb}}^k(\mu)\} \in \mathbb{V}_{\text{rb}}^N, 0 \le k \le k_{max}$, which satisfies (3.7).

Fix k and let $\{\mathbf{u}_{k,i}^\mu\}_{i=1}^N$ be the coefficients of the representation of $u_{\text{rb}}^k(\mu)$ in the reduced basis $\mathbb{V}_{\text{rb}}$ (see (2.6) in the discussion of the glioma model). Then we test (3.7) with all $\phi = \xi_j, 1 \le j \le N$ and we obtain a system of N equations for $\{\mathbf{u}_{k,i}^\mu\}_{i=1}^N$ in terms of the coefficients of the representation on the previous $k-1$-st time layer, $\{\mathbf{u}_{k-1,i}^\mu\}_{i=1}^N$

$$
\begin{aligned}
\sum_{i=1}^N \mathbf{u}_{k,i}^\mu\langle\xi_i,\xi_j\rangle + \theta\tau\sum_{i=1}^N \mathbf{u}_{k,i}^\mu a(\xi_i,\xi_j) &= \sum_{i=1}^N \mathbf{u}_{k-1,i}^\mu\langle\xi_i,\xi_j\rangle\\
&- \tau L^{k-1}(\xi_j) - (1-\theta)\tau\sum_{i=1}^N \mathbf{u}_{k-1,i}^\mu a(\xi_i,\xi_j), \quad \forall j = 1,\dots N\ .
\end{aligned}
\tag{3.8}
$$

Here in the right-hand side we let

$$
L^{k-1}(\xi_j;\mu) = p_1^{(k-1)}(\xi_j) - \mu p_2^{(k-1)}(\xi_j) - p_3^{(k-1)}(\xi_j),
$$

where the individual summands are defined as

$$
\begin{aligned}
p_1^{(k-1)}(\xi_j) &= \sum_{i=1}^{N} \mathbf{u}_{k-1,i}^{\mu} \langle \beta(\cdot)\xi_i, \xi_j \rangle \\
p_2^{(k-1)}(\xi_j) &= \sum_{i=1}^{N} \mathbf{u}_{k-1,i}^{\mu} \langle \gamma(\cdot)\xi_i, \xi_j \rangle \\
p_3^{(k-1)}(\xi_j) &= \rho_{k-1} \sum_{i=1}^{N} \mathbf{u}_{k-1,i}^{\mu} \langle \xi_i, \xi_j \rangle \quad \text{with} \\
\rho_{k-1} &= \int_{\Omega} u_{\mathrm{rb}}^{k-1}(\mu)\ dxdy = \sum_{i=1}^{N} \mathbf{u}_{k-1,i}^{\mu} \int_{\Omega} \xi_i\ dxdy\ .
\end{aligned}
$$

Thus, we can rewrite the linear problem in matrix notation:

$$
(\mathbb{M} + \theta\tau\mathbb{A})\mathbf{u}_k^{\mu} = (\mathbb{M} - (1-\theta)\tau\mathbb{A})\mathbf{u}_{k-1}^{\mu} - \tau L_{k-1}^{\mu}\mathbf{u}_{k-1}^{\mu} \tag{3.10}
$$

where

$$
L_{k-1}^{\mu} = \mathbb{P}_1 - \mu\mathbb{P}_2 - \rho_{k-1}\mathbb{M}\ .
$$

and $\mathbb{M}, \mathbb{A}, \mathbb{P}_1, \mathbb{P}_2$ are matrices that can be computed and stored during the *offline stage* because they are independent of μ. They are defined as

$$
\begin{aligned}
\mathbb{M} : (\mathbb{M})_{ij} &\overset{\mathsf{def}}{=} \langle \xi_i, \xi_j \rangle, \\
\mathbb{A} : (\mathbb{A})_{ij} &\overset{\mathsf{def}}{=} a(\xi_i, \xi_j). \\
\mathbb{P}_1 : (\mathbb{P}_1)_{ij} &\overset{\mathsf{def}}{=} \langle \beta(\cdot)\xi_i, \xi_j \rangle. \\
\mathbb{P}_2 : (\mathbb{P}_2)_{ij} &\overset{\mathsf{def}}{=} \langle \gamma(\cdot)\xi_i, \xi_j \rangle\ .
\end{aligned} \tag{3.11}
$$

Note that due to the linearity of the integral, we may compute the non-local term ρ_{k-1} using the expansion in the reduced basis $\mathbb{V}_{\mathrm{rb}}^N$. An appropriate quadrature rule should be chosen to approximate the integrals of ξ_i over Ω. Hence in addition to the parameter-independent objects that must be stored during the *offline stage* of solving (3.3) (the matrices $\mathbb{M}, \mathbb{A}, \mathbb{P}_1, \mathbb{P}_2$), for this integro-differential equation we must also store the integrals of the RB basis elements $\mathbb{I}_i \overset{\mathsf{def}}{=} \int_{\Omega} \xi_i\ dxdy$ in order to compute the value of ρ_k as a linear combination of $\mathbb{I}_i$. Finally, the solution resulting in the reduced basis approximation is recovered as $U_{\mathrm{rb}}(\mu) = \{u_{\mathrm{rb}}^k(\mu)\}, u_{\mathrm{rb}}^k(\mu) \overset{\mathsf{def}}{=} \mathbb{V}\mathbf{u}_k^{\mu}$.

3.3.2 A posteriori error analysis for the IMEX-θ scheme

The construction of the reduced basis from the snapshots will be performed during the *offline phase* via the POD-greedy algorithm described in the Introduction. The choice of points in the parameter training set Ξ_{train} shall be assumed by some appropriate sampling procedure. We shall use a greedy algorithm with a posteriori error estimates for the approximation error between the truth solution (3.5) and the reduced basis solution (3.7) which will be derived in Section 3.3.3.

The computation of a particular RB approximation $U_{\mathrm{rb}}(\mu)$ for a given μ is done in the *online phase*. There its coefficients in the reduced basis expansion are computated,

and the solution is assembled via the RB matrix $\mathbb{V} = [\xi_i]$. The algebraic problem of the reduced basis method for the θ-scheme has been described in Section 3.3.1.

As in Section 2.3.2 in order to construct an efficient POD-greedy algorithm we need an *a posteriori* estimator for the error between the truth approximation $u_h(\mu)$ and the reduced basis solution $u_{\mathrm{rb}}(\mu)$. In the context of the model (3.3), we have no dependence on μ for the bilinear form $a(\cdot, \cdot; \mu)$

$$a(u, v; \mu) = \alpha \int_\Omega \nabla u \nabla v \; dxdy \; .; .$$

For clarity we shall drop μ from the notation of the solution and let $\{u_{\mathrm{rb}}^k\}$ be the reduced basis solution at layer k.

Here we develop *a posteriori* error analysis to assess the error $e_k(\mu)$. for the particular model (3.3). However, unlike the model considered in Chapter 2, the non-linear term F describing the growth with crowding effects is not Lipschitz-continuous. Hence, we cannot proceed on the basis of Proposition 1 to obtain an estimate on the approximation error, based solely on the Lipschitz constant. Instead, we can use the properties of the solutions to (3.3) subject to certain initial values which nevertheless encompass all biologically-relevant scenarios.

We recall the following results on *a priori* bounds of the solution to (3.3).

Lemma 2. *Denote* $\tilde{\beta} \stackrel{\text{def}}{=} \sup_{(x,y)\in\Omega} \beta(x, y)$. *Let* $u(0, \cdot) = u_0$ *be the initial data to* (3.3) *such that* $\|u_0\|_{L^1} < \tilde{\beta}$. *Then the solution of* (3.3) *satisfies the following*

$$\|u(t, \cdot)\|_{L^1} \leq \tilde{\beta}, \quad \forall t > 0 \; .$$

Proof. Integrate both sides of (3.3) over Ω :

$$\frac{\partial}{\partial t} \int_\Omega u dxdy = \int_\Omega (\beta(x, y) - \rho(t))u dxdy - \int_\Omega \gamma(x)\mu u dxdy + \alpha \int_\Omega \Delta u dxdy$$

The Neumann boundary conditions imply

$$\int_\Omega \Delta u \; dxdy = \oint_{\partial\Omega} \nabla u \; d\mathbf{n} = 0, \tag{3.12}$$

which leads to

$$\begin{aligned} \frac{\partial}{\partial t}\rho = \int_\Omega (\beta(x, y) - \rho(t))u \; dxdy - \int_\Omega \gamma(x)\mu u \; dxdy \\ \leq \left(\sup_{(x,y)\in\Omega} \beta(x, y) - \rho \right) \rho - \left(\inf_{\substack{x\in\Omega \\ \mu\in\mathcal{M}}} \gamma(x)\mu \right) \rho = (\tilde{\beta} - \rho)\rho. \end{aligned}$$

because $\inf_{x\in\Omega,\mu\in\mathcal{M}} \gamma(x)\mu = 0$, see (3.4b). The above equation on the right-hand side is a logistic growth law, which means that if $\rho(0) \leq \tilde{\beta}$, then $\rho(t) \leq \tilde{\beta}, \forall t > 0$. □

Even if the nonlinearity f is not Lipschitz, we can still use the results of Lemma 2 to establish a Lipschitz-type growth. However, we may do the following computation for

functions $v, v' \in L^1(\Omega)$ for a fixed μ (we shall omit it from the equations for the sake of clarity):

$$\begin{aligned}|f(v(x,y)) - f(v'(x,y))| \\ &= \left| \left(\beta(x,y) - \gamma(\mu) - \int_\Omega v \right) v(x,y) - \left(\beta(x,y) - \gamma(\mu) - \int_\Omega v' \right) v'(x,y) \right| \\ &\leq \tilde{\beta} |v(x,y) - v'(x,y)| + \left| (\int_\Omega v) v(x,y) - (\int_\Omega v') v'(x,y) \right| \ .\end{aligned}$$

Note that

$$\begin{aligned}\left| v(x,y) \int_\Omega v - v'(x,y) \int_\Omega v' \right| \\ &= \left| (v(x,y) - v'(x,y)) \int_\Omega v + v'(x,y) \int_\Omega (v - v') \right| \\ &\leq |v(x,y) - v'(x,y)| \|v\|_{L^1} + |v'(x,y)| \|v - v'\|_{L^1} \ .\end{aligned}$$

Thus, we obtain

$$\begin{aligned}|f(v(x,y)) - f(v'(x,y))| \leq \tilde{\beta} |v(x,y) - v'(x,y)| \\ &+ |v(x,y) - v'(x,y)| \|v\|_{L^1} + |v'(x,y)| \|v - v'\|_{L^1} \quad (3.13)\end{aligned}$$

Now consider the truth and the RB solutions u^k_{rb}, u^k_h whose initial data meet the conditions of Lemma 2. Because $\dim \mathbb{V}_h = N_h$, $u^k_{\mathrm{rb}}, u^k_h \in L^1(\Omega)$ and, moreover, the Lemma establishes their L^1-norms are globally bounded. Since the nonlinearity in our problem satisfies (3.13), in combination with the triangle inequality $\|v - v'\|_{L^1} \leq \|v\|_{L^1} + \|v'\|_{L^1}$ it yields

$$|f(u^k_h; \mu) - f(^k_{\mathrm{rb}}; \mu)| \leq 2\tilde{\beta} |u^k_h - u^k_{\mathrm{rb}}| + 2\tilde{\beta} |u^k_{\mathrm{rb}}|, \quad \forall (x,y) \in \Omega \ . \tag{3.14}$$

We remark that the restriction on the initial data given in the statement of Lemma 2 is biologically relevant. If the initial data did not satisfy the condition, the dynamics of the tumour volume would be decreasing as the tumour would be beyond the carrying capacity of the microenvironment, even if no therapy is applied ($\mu = 0$).

Next we state the following *a posteriori* error estimate:

Proposition 2. *Let $\ell_{sup} = 2\tilde{\beta}$. Suppose that f fulfils the Lipschitz-type growth condition* (3.14) *Then letting $\tilde{R}^{k+1}(\mu) \overset{\text{def}}{=} \ell_{sup} \|u^k_{\mathrm{rb}}(\mu)\|_{L^2} + \|r^{k+1}(\mu)\|_*$ with the residual r defined in* (2.17)*, we have the following estimates on the approximation error between the truth and the reduced basis solution $e_k(\mu) = u^k_h(\mu) - u^k_{\mathrm{rb}}(\mu)$ for the IMEX-θ scheme:*

(i) Let $\theta \geq 1/2$. Then

$$\|e_k\|^2_{L^2} \leq \frac{\tau}{a_{min}} \sum_{i=1}^{k} \left(1 + \tau \frac{\ell^2_{sup}}{a_{min}} \right)^{k-i} \tilde{R}^i(\mu)^2 \ .$$

(ii) Let $\theta < 1/2$. Assume the time step τ and triangulation $\mathcal{T}_h$ satisfy

$$\tau \left(1 + \frac{c_\Omega}{h^2} \right) < \frac{2a_{min}}{(1 - 2\theta) a^2_{max}} \ .$$

Then

$$\|e_k\|_{L^2}^2 \leq 2\tau C_{\epsilon,\eta} \sum_{i=1}^{k} (1 + 2\tau \ell_{sup}^2 C_{\epsilon,\eta})^{k-i} \tilde{R}^i(\mu)^2 \,, \tag{3.15}$$

for appropriately chosen $C_{\epsilon,\eta}$ which is independent of τ, h, μ.

Proof. The idea of the proof follows that of Proposition 1. We use the form of the residual r (2.17) but we modify the resulting estimator which is labeled $\tilde{R}$. The second major difference between the derivation in Proposition 1 and here lies in the treatment of the term $|f(u_h^k;\mu) - f(_{\rm rb}^k;\mu)|$ which arises in the evolution equation for the approximation error.

Using the Lipschitz-type estimate of f given by (3.14), Hölder's inequality, and the embedding $H^1(\Omega) \subset L^2(\Omega)$:

$$\begin{aligned}\langle f(u_h^k;\mu) - f(u_{\rm rb}^k;\mu), \phi\rangle &\leq \int_\Omega |f(u_h^k;\mu) - f(u_{\rm rb}^k;\mu)||\phi| \; dxdy \\ &\leq \ell_{sup}(\| \underbrace{u_h^k - u_{\rm rb}^k}_{=e_k} \|_{L^2} + \|u_{\rm rb}^k\|_{L^2})\|\phi\|_{L^2} \leq \ell_{sup}(\|e_k\|_{L^2} + \|u_{\rm rb}^k\|_{L^2})\|\phi\|_{H^1} \,. \end{aligned} \tag{3.16}$$

with the appropriate choice $\ell_{sup} = 2\tilde{\beta}$.

Hence, when f has Lipschitz-type growth (3.14), we proceed as follows. With a test function $\phi = \theta e_{k+1} + (1-\theta)e_k$, using (3.16) the right-hand side of (2.18) can be bounded by

$$\begin{aligned}&\langle f(u_h^k;\mu) - f(u_{\rm rb}^k;\mu), \theta e_{k+1} + (1-\theta)e_k\rangle + r^{k+1}(\theta e_{k+1} + (1-\theta)e_k;\mu) \\ &\qquad \leq (\ell_{sup}(\|e_k\|_{L^2} + \|u_{\rm rb}^k\|_{L^2}) + \|r^{k+1}(\mu)\|_*) \cdot \|\theta e_{k+1} + (1-\theta)e_k\|_{H_1} \,.\end{aligned}$$

If we let $\tilde{R}^{k+1}(\mu) \stackrel{\text{def}}{=} \ell_{sup}\|u_{\rm rb}^k\|_{L^2} + \|r^{k+1}(\mu)\|_*$, we may use the analysis from Proposition 1 to establish the bounds. In fact, using Young's inequality, for all $0 < \epsilon \leq 1$ we have

$$\begin{aligned}&(\ell_{sup}(\|e_k\|_{L^2} + \|u_{\rm rb}^k\|_{L^2}) + \|r^{k+1}(\mu)\|_*) \cdot \|\theta e_{k+1} + (1-\theta)e_k\|_{H_1} \\ &\qquad \leq \frac{1}{4\epsilon a_{min}}(\ell_{sup}\|e_k\|_{L^2} + \tilde{R}^{k+1}(\mu))^2 + \epsilon a_{min}\|\theta e_{k+1} + (1-\theta)e_k\|_{H_1}^2 \\ &\qquad\qquad \leq \frac{1}{2\epsilon a_{min}}(\ell_{sup}^2\|e_k\|_{L^2}^2 + \tilde{R}^{k+1}(\mu)^2) + \epsilon a_{min}\|\theta e_{k+1} + (1-\theta)e_k\|_{H_1}^2 \,.\end{aligned}$$

Combining these estimates we see that

$$\begin{aligned}&\frac{1}{2\tau}\|e_{k+1}\|_{L^2}^2 - \frac{1}{2\tau}\|e_k\|_{L^2}^2 + \frac{1}{\tau}\left(\theta - \frac{1}{2}\right)\|e_{k+1} - e_k\|_{L^2}^2 + a_{min}\|\theta e_{k+1} + (1-\theta)e_k\|_{H^1}^2 \\ &\qquad \leq \frac{1}{2\epsilon a_{min}}(\ell_{sup}^2\|e_k\|_{L^2}^2 + \tilde{R}^{k+1}(\mu)^2) + \epsilon a_{min}\|\theta e_{k+1} + (1-\theta)e_k\|_{H_1}^2,\end{aligned} \tag{3.17}$$

for all $0 < \epsilon \leq 1$.

With this estimate we continue as in the proof of Proposition 1 to establish the results in the statement for the cases $\theta \leq 1/2$ and $1/2 < \theta < 1$. □

3.3.3 Computing the a posteriori error estimator

Proposition 2 provides an a posteriori error estimator for the approximation error $e_k(\mu)$ between the truth solution (2.3) and the reduced basis solution (2.5) at time layer $k\tau$ of the form

$$\|e_k(\mu)\|_{L^2}^2 \leq \Delta_k(\mu) = \tau C_1 \sum_{i=1}^{k} C_2^{k-i} (\tilde{R}^i(\mu))^2 \tag{3.18}$$

with $C_1 > 0, C_2 > 1$. By virtue of (3.18), for a given solution trajectory $U_h(\mu)$, the quantity $\Delta(\mu)$ attains its maximum at $k = k_{max}$ [9]. Hence it suffices to set as the *a posteriori* error estimator for the scheme (2.5):

$$\Delta(\mu) \stackrel{\text{def}}{=} \Delta_{k_{max}}(\mu) \ .$$

It remains to describe an efficient manner to compute $\Delta(\mu)$. Recall the definition of the residual $\tilde{R}^{k+1}(\mu) \stackrel{\text{def}}{=} \ell_{sup}\|u_{\text{rb}}^k(\mu)\|_{L^2} + \|r^{k+1}(\mu)\|_*$ from Proposition 2, with $\tilde{r}$ given by (2.17). We now use the affine dependence of the reaction term in (3.3) to decompose the norm of the residual $\|r^k(\mu)\|_*$ into elements which are readily computed during the online phase.

We substitute the formula for the bilinear form a and nonlinearity f into the expansion of r^k. Using the RB expansion of u_{rb}^k, given in (2.6), we have

$$\rho_k = \sum_{i=1}^{N} \mathbf{u}_{k,i}^{\mu} \int_{\Omega} \xi_i \ dxdy \ ,$$

and can rewrite r^{k+1} as

$$\begin{aligned} r^{k+1}(\phi;\mu) &= \langle f(u_{\text{rb}}^k), \phi\rangle - \frac{1}{\tau}\langle u_{\text{rb}}^{k+1} - u_{\text{rb}}^k, \phi\rangle - a(\theta u_{\text{rb}}^{k+1} + (1-\theta)u_{\text{rb}}^k, \phi) \\ &= \sum_{i=1}^{N} \mathbf{u}_{k,i}^{\mu} \langle \beta(\cdot)\xi_i, \phi\rangle - \rho_k \sum_{i=1}^{N} \mathbf{u}_{k,i}^{\mu} \langle \xi_i, \phi\rangle - \mu \sum_{i=1}^{N} \mathbf{u}_{k,i}^{\mu} \langle \gamma(\cdot)\xi_i, \phi\rangle \\ &- \sum_{i=1}^{N} \frac{\mathbf{u}_{k+1,i}^{\mu} - \mathbf{u}_{k,i}^{\mu}}{\tau} \langle \xi_i, \phi\rangle - \sum_{i=1}^{N} (\theta \mathbf{u}_{k+1,i}^{\mu} + (1-\theta)\mathbf{u}_{k,i}^{\mu}) a(\xi_i, \phi), \quad \forall \phi \in \mathbb{V}_h \ . \end{aligned}$$

Following [12] we introduce the coefficient vector $\mathbf{r}^k(\mu) \in \mathbb{R}^{5N}$

$$\mathbf{r}^k(\mu) \stackrel{\text{def}}{=} (\mathbf{u}_{k,i}^{\mu}, -\rho_k \mathbf{u}_{k,i}^{\mu}, -\mu \mathbf{u}_{k,i}^{\mu}, -\frac{\mathbf{u}_{k+1,i}^{\mu} - \mathbf{u}_{k,i}^{\mu}}{\tau}, (\theta \mathbf{u}_{k+1,i}^{\mu} + (1-\theta)\mathbf{u}_{k,i}^{\mu}))^T$$

and the vector of forms $\mathfrak{R} \in (\mathbb{V}'_{\text{rb}})^{5N}$

$$\mathfrak{R} \stackrel{\text{def}}{=} (\{\langle \beta(\cdot)\xi_i, \cdot\rangle\}_{i=1}^N, \{\langle \xi_i, \cdot\rangle\}_{i=1}^N, \{\langle \gamma(\cdot)\xi_i, \phi\rangle\}_{i=1}^N, \{\langle \xi_i, \cdot\rangle\}_{i=1}^N, \{a(\xi_i, \cdot)\}_{i=1}^N) \ , \tag{3.19}$$

leading to the following representation of the residual $r^{k+1}(\phi;\mu)$:

$$r^{k+1}(\phi;\mu) = \sum_{j=1}^{5N} \mathbf{r}_j^k(\mu) \mathfrak{R}_j(\phi), \quad \forall \phi \in \mathbb{V}_h \ . \tag{3.20}$$

Let $\hat{r}_j \in \mathbb{V}_h$ denote the Riesz representation of the functional $\mathfrak{R}_j$ so that $\langle \hat{r}_j, \phi \rangle_{H^1} = \mathfrak{R}_j(\phi), \forall \phi \in \mathbb{V}_h, j = 1, \dots 5N$ (observe that each $\hat{r}_j$ is independent of the time layer k). We obtain the following relation for the Riesz representation of r^{k+1} and its norm

$$\tilde{r}^{k+1}(\mu) = \sum_{j=1}^{5N} \mathbf{r}_j^k(\mu)\hat{r}_j \Rightarrow \|\tilde{r}^{k+1}(\mu)\|_{H^1}^2 = \sum_{j=1}^{5N}\sum_{j'=1}^{5N} \mathbf{r}_j^k(\mu)\mathbf{r}_{j'}^k(\mu)\langle \hat{r}_j, \hat{r}_{j'} \rangle_{H^1} \ .$$

Observe that some elements of the vector $\mathfrak{R}$ are the same. To find $\hat{r}_j$, we follow the same steps from Section 2.3.3.

Chapter 4

Conclusion and Outlook

We have derived *a posteriori* estimators for the approximation error that should be used in a POD-greedy algorithm for constructing reduced basis for two models describing tumour growth (2.1) and phenotype evolution inside a tumour (3.3). These models are based on reaction-diffusion equations which permits the use of the first-order in time IMEX-θ scheme as a suitable numerical scheme for time integration. The *a posteriori* error estimators are closely linked to the specific problem, as has been noted in the reduced basis literature.

The described algorithms for the reduced basis construction shall be implemented in the finite element library `FreeFem++` [11] to test the performance of the RB method in approximating the high-fidelity solutions to the considered problems.

However, second-order schemes are necessary to accurately approximate models such as (3.2) in their full generality. This is due to the presence of nonzero advection terms which require caution in the numerical treatment. In addition, the construction of a reduced basis approximation may require modification of the algorithm, as turns out to be the case for transport-dominated problems [7].

We test the performance of several second-order IMEX methods on equation (3.3). The chosen parameters are: mutation rate $\alpha = 10^{-5}$, proliferation rate is $\beta(x, y) = 0.03 + 0.25y(1 - y^2) + 0.05(1 - x)x$, death rate $\gamma = 0.02$, $\mu = 0$. The initial condition is

$$u_0 \stackrel{\text{def}}{=} u(x, y, 0) = 0.5|\sin(5\pi x)\sin(5\pi y)|.$$

The methods (1.5)-(1.7) are 2-step methods and not self-starting, so we initialise the data for the second step u_1 by using an IMEX-θ scheme with $\theta = 2/3$. Therefore, this peculiarity must be taken into account when developing *a posteriori* error estimators for second-order IMEX methods.

The FE space is with Lagrangian-P2 elements on a Square mesh : with 2601 vertices, 5000 triangles and 200 boundary edges, time step $\tau = 5$, stop criterion for convergence to stationary solution : $\|u_{k+1} - u_k\|_\infty < 10^{-4}$. Computation is performed in `FreeFem++`. Results of the test are summarised in Table 4.1.

As expected, the IMEX-θ scheme (1.4) is the fastest because it is a one-step scheme. It shall be used for the numerical implementation of the considered parabolic problems based on the IMEX-θ scheme. It would be interesting to compare the performance of the RB method for the same problems based on some second-order IMEX scheme, once *a posteriori* estimators for those are available.

Table 4.1: Numerical test.

IMEX method	(1.4) $\theta = 2/3$	(1.5)	(1.6)	(1.7)
compile (s)	0.005897	0.010604	0.006063	0.006091
execution (s)	21.5779	38.5859	42.404	70.0746

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Bibliography

[1] U. M. Ascher, S. J. Ruuth, and B. T. R. Wetton. Implicit-explicit methods for time-dependent partial differential equations. *SIAM J. Numerical Analysis*, 32(3):797–823, 1995.

[2] I. Babuška, J. Whiteman, and T. Strouboulis. *Finite Elements: An Introduction to the Method and Error Estimation.* Oxford University Press, 2010.

[3] R. H. Chisholm, T. Lorenzi, A. Lorz, A. K. Larsen, L. Almeida, A. Escargueil, and J. Clairambault. Emergence of drug tolerance in cancer cell populations: an evolutionary outcome of selection, non-genetic instability and stress-induced adaptation. *Cancer Research*, 75:930, 2015.

[4] O. Christensen. *An Introduction to Frames and Riesz Bases.* Birkhäuser, 2003.

[5] P. G. Ciarlet. *The Finite Element Method for Elliptic Problems.* Classics in Applied Mathematics. SIAM, 2002.

[6] W. Dahmen, C. Huang, G. Kutyniok, W.-Q. Lim, C. Schwab, and G. Welper. Efficient resolution of anisotropic structures. In S. Dahlke, W. Dahmen, M. Griebel, W. Hackbusch, K. Ritter, R. Schneider, C. Schwab, and H. Yserentant, editors, *Extraction of Quantifiable Information from Complex Systems*, Lecture Notes in Computational Science and Engineering, pages 25–51. Springer International Publishing, 2014.

[7] W. Dahmen, C. Plesken, and G. Welper. Double greedy algorithms: Reduced basis methods for transport dominated problems. *ESAIM: Mathematical Modelling and Numerical Analysis - Modélisation Mathématique et Analyse Numérique*, 48(3):623–663, 2014.

[8] M. A. Grepl and A. T. Patera. A posteriori error bounds for reduced-basis approximations of parametrized parabolic partial differential equations. *ESAIM: Mathematical Modelling and Numerical Analysis*, 39(1):157–181, 2005.

[9] B. Haasdonk and M. Ohlberger. Reduced basis method for finite volume approximations of parametrized linear evolution equations. *ESAIM: Mathematical Modelling and Numerical Analysis*, 42:277–302, 2008.

[10] B. Haasdonk, M. Ohlberger, and G. Rozza. A reduced basis method for evolution schemes with parameter-dependent explicit operators. *Electronic Transactions on Numerical Analysis*, 32:145–168, 2008.

[11] F. Hecht. New development in `FreeFem++`. *J. Numerical Mathematics*, 20:251–265, 2012.

[12] J. S. Hesthaven, G. Rozza, and B. Stamm. *Certified Reduced Basis Methods for Parametrized Partial Differential Equations*. Springer International Publishing, 2016.

[13] P. Magal and G. F. Webb. Mutation, selection and recombination in a model of phenotype evolution. *Discrete & Continuous Dynamical Systems B*, 6(1):221–236, 2000.

[14] J. D. Murray. *Mathematical Biology II: Spatial Models and Biomedical Applications*. Springer-Verlag Berlin Heidelberg, 3rd edition, 2003.

[15] A. Quarteroni, A. Manzoni, and F. Negri. *Reduced Basis Methods for Partial Differential Equations*. Springer International Publishing, 2016.

[16] A. Quarteroni and A. Valli. *Numerical Approximation of Partial Differential Equations*. Springer-Verlag Berlin Heidelberg, 2008.

[17] V. Thomée. *Galerkin Finite Element Methods for Parabolic Problems*. Springer Verlag Berlin Heidelberg, 2nd edition, 2006.

[18] K. Urban, S. Volkwein, and O. Zeeb. Greedy sampling using nonlinear optimization. In A. Quarteroni and G. Rozza, editors, *Reduced Order Methods for Modeling and Computational Reduction*, pages 137–157. Springer International Publishing, 2014.